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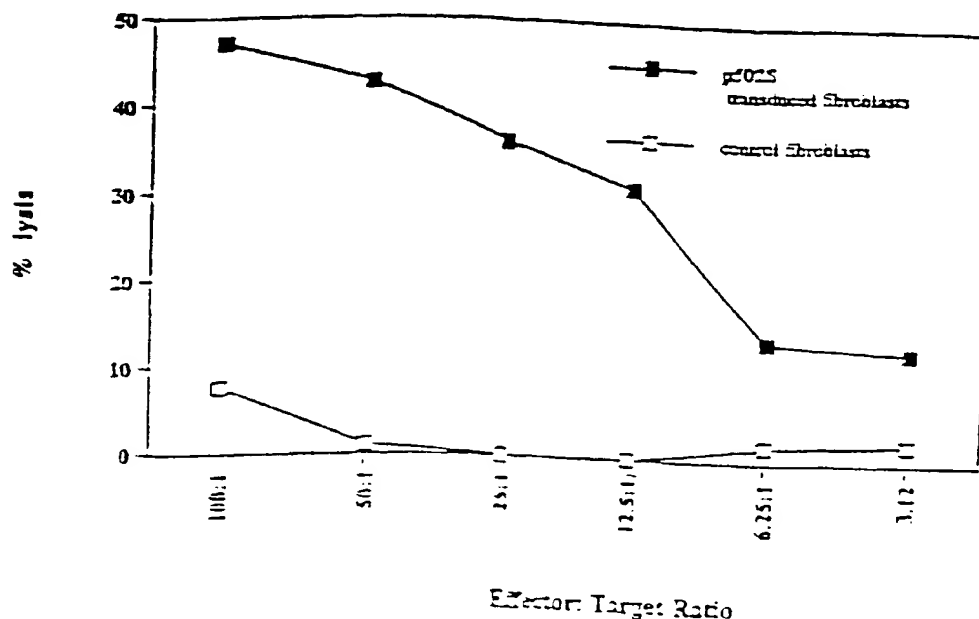
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[Continued on next page]

(54) Title: COMPOSITIONS AND METHODS FOR THE THERAPY AND DIAGNOSIS OF PROSTATE CANCER



(57) Abstract: Compositions and methods for the therapy and diagnosis of cancer, particularly prostate cancer, are disclosed. Illustrative compositions comprise one or more prostate-specific polypeptides, immunogenic portions thereof, polynucleotides that encode such polypeptides, antigen presenting cell that expresses such polypeptides, and T cells that are specific for cells expressing such polypeptides. The disclosed compositions are useful, for example, in the diagnosis, prevention and/or treatment of diseases, particularly prostate cancer.

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## COMPOSITIONS AND METHODS FOR THE THERAPY AND DIAGNOSIS OF PROSTATE CANCER

### 5 TECHNICAL FIELD OF THE INVENTION

The present invention relates generally to therapy and diagnosis of cancer, such as prostate cancer. The invention is more specifically related to polypeptides, comprising at least a portion of a prostate-specific protein, and to polynucleotides encoding such polypeptides. Such polypeptides and polynucleotides  
10 are useful in pharmaceutical compositions, *e.g.*, vaccines, and other compositions for the diagnosis and treatment of prostate cancer.

### BACKGROUND OF THE INVENTION

Cancer is a significant health problem throughout the world. Although Cancer is a significant health problem throughout the world. Although advances have  
15 been made in detection and therapy of cancer, no vaccine or other universally successful method for prevention or treatment is currently available. Current therapies, which are generally based on a combination of chemotherapy or surgery and radiation, continue to prove inadequate in many patients.

Prostate cancer is the most common form of cancer among males, with  
20 an estimated incidence of 30% in men over the age of 50. Overwhelming clinical evidence shows that human prostate cancer has the propensity to metastasize to bone, and the disease appears to progress inevitably from androgen dependent to androgen refractory status, leading to increased patient mortality. This prevalent disease is currently the second leading cause of cancer death among men in the U.S.

25 In spite of considerable research into therapies for the disease, prostate cancer remains difficult to treat. Commonly, treatment is based on surgery and/or radiation therapy, but these methods are ineffective in a significant percentage of cases. Two previously identified prostate specific proteins - prostate specific antigen (PSA)

and prostatic acid phosphatase (PAP) - have limited therapeutic and diagnostic potential. For example, PSA levels do not always correlate well with the presence of prostate cancer, being positive in a percentage of non-prostate cancer cases, including benign prostatic hyperplasia (BPH). Furthermore, PSA measurements correlate with prostate volume, and do not indicate the level of metastasis.

In spite of considerable research into therapies for these and other cancers, prostate cancer remains difficult to diagnose and treat effectively. Accordingly, there is a need in the art for improved methods for detecting and treating such cancers. The present invention fulfills these needs and further provides other related advantages.

## 10 SUMMARY OF THE INVENTION

In one aspect, the present invention provides polynucleotide compositions comprising a sequence selected from the group consisting of:

(a) sequences provided in SEQ ID NO: 1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 and 384-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-626, 630, 631, 634, 636, 639-655, 674, 680, 681, 711, 713, 716, 720-722, 735, 737-739, 751, 753, 764, 765, 773-776 and 786-788;

(b) complements of the sequences provided in SEQ ID NO: 1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 and 384-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-626, 630, 631, 634, 636, 639-655, 674, 680, 681, 711, 713, 716, 720-722, 735, 737-739, 751, 753, 764, 765, 773-776 and 786-788;

(c) sequences consisting of at least 20 contiguous residues of a sequence provided in SEQ ID NO: 1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 and 384-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-626, 630, 631, 634, 636, 639-655, 674, 680, 681, 711, 713, 716, 720-722, 735, 737-739, 751, 753, 764, 765, 773-776 and 786-788;

(d) sequences that hybridize to a sequence provided in SEQ ID NO: 1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375,

381, 382 and 384-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-626, 630, 631, 634, 636, 639-655, 674, 680, 681, 711, 713, 716, 720-722, 735, 737-739, 751, 753, 764, 765, 773-776 and 786-788, under moderately stringent conditions;

5 (e) sequences having at least 75% identity to a sequence of SEQ ID NO: 1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 and 384-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-626, 630, 631, 634, 636, 639-655, 674, 680, 681, 711, 713, 716, 720-722, 735, 737-739, 751, 753, 764, 765, 773-776 and 786-788;

10 (f) sequences having at least 90% identity to a sequence of SEQ ID NO: 1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 and 384-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-626, 630, 631, 634, 636, 639-655, 674, 680, 681, 711, 713, 716, 720-722, 735, 737-739, 751, 753, 764, 765, 773-776 and 786-788; and

15 (g) degenerate variants of a sequence provided in SEQ ID NO: 1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 and 384-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-626, 630, 631, 634, 636, 639-655, 674, 680, 681, 711, 713, 716, 720-722, 735, 737-739, 751, 753, 764, 765, 773-776 and 786-788.

20 In one preferred embodiment, the polynucleotide compositions of the invention are expressed in at least about 20%, more preferably in at least about 30%, and most preferably in at least about 50% of prostate tissue samples tested, at a level that is at least about 2-fold, preferably at least about 5-fold, and most preferably at least about 10-fold higher than that for other normal tissues.

25 The present invention, in another aspect, provides polypeptide compositions comprising an amino acid sequence that is encoded by a polynucleotide sequence described above.

The present invention further provides polypeptide compositions comprising an amino acid sequence selected from the group consisting of sequences  
30 recited in SEQ ID NO: 112-114, 172, 176, 178, 327, 329, 331, 336, 339, 376-380, 383,

477-483, 496, 504, 505, 519, 520, 522, 525, 527, 532, 534, 537-551, 553-568, 573-586, 588-590, 592, 627-629, 632, 633, 635, 637, 638, 656-671, 675, 683, 684, 710, 712, 714, 715, 717-719, 723-734, 736, 740-750, 752, 754, 755, 766-772, 777-785 and 789-791.

In certain preferred embodiments, the polypeptides and/or  
5 polynucleotides of the present invention are immunogenic, *i.e.*, they are capable of eliciting an immune response, particularly a humoral and/or cellular immune response, as further described herein.

The present invention further provides fragments, variants and/or derivatives of the disclosed polypeptide and/or polynucleotide sequences, wherein the  
10 fragments, variants and/or derivatives preferably have a level of immunogenic activity of at least about 50%, preferably at least about 70% and more preferably at least about 90% of the level of immunogenic activity of a polypeptide sequence set forth in SEQ ID NO: 112-114, 172, 176, 178, 327, 329, 331, 336, 339, 376-380, 383, 477-483, 496, 504, 505, 519, 520, 522, 525, 527, 532, 534, 537-551, 553-568, 573-586, 588-590, 592, 627-  
15 629, 632, 633, 635, 637, 638, 656-671, 675, 683, 684, 710, 712, 714, 715, 717-719, 723-734, 736, 740-750, 752, 754, 755, 766-772, 777-785 or 789-791, or a polypeptide sequence encoded by a polynucleotide sequence set forth in SEQ ID NO: 1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 and 384-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-626,  
20 630, 631, 634, 636, 639-655, 674, 680, 681, 711, 713, 716, 720-722, 735, 737-739, 751, 753, 764, 765, 773-776 and 786-788.

The present invention further provides polynucleotides that encode a polypeptide described above, expression vectors comprising such polynucleotides and host cells transformed or transfected with such expression vectors.

25 Within other aspects, the present invention provides pharmaceutical compositions comprising a polypeptide or polynucleotide as described above and a physiologically acceptable carrier.

Within a related aspect of the present invention, pharmaceutical compositions, *e.g.*, vaccine compositions, are provided for prophylactic or therapeutic  
30 applications. Such compositions generally comprise an immunogenic polypeptide or

polynucleotide of the invention and an immunostimulant, such as an adjuvant, together with a physiologically acceptable carrier.

The present invention further provides pharmaceutical compositions that comprise: (a) an antibody or antigen-binding fragment thereof that specifically binds to  
5 a polypeptide of the present invention, or a fragment thereof; and (b) a physiologically acceptable carrier.

Within further aspects, the present invention provides pharmaceutical compositions comprising: (a) an antigen presenting cell that expresses a polypeptide as described above and (b) a pharmaceutically acceptable carrier or excipient. Illustrative  
10 antigen presenting cells include dendritic cells, macrophages, monocytes, fibroblasts and B cells.

Within related aspects, pharmaceutical compositions are provided that comprise: (a) an antigen presenting cell that expresses a polypeptide as described above and (b) an immunostimulant.

15 The present invention further provides, in other aspects, fusion proteins that comprise at least one polypeptide as described above, as well as polynucleotides encoding such fusion proteins, typically in the form of pharmaceutical compositions, e.g., vaccine compositions, comprising a physiologically acceptable carrier and/or an immunostimulant. The fusions proteins may comprise multiple immunogenic  
20 polypeptides or portions/variants thereof, as described herein, and may further comprise one or more polypeptide segments for facilitating and/or enhancing the expression, purification and/or immunogenicity of the polypeptide(s).

Within further aspects, the present invention provides methods for stimulating an immune response in a patient, preferably a T cell response in a human  
25 patient, comprising administering a pharmaceutical composition described herein. The patient may be afflicted with prostate cancer, in which case the methods provide treatment for the disease, or a patient considered to be at risk for such a disease may be treated prophylactically.

Within further aspects, the present invention provides methods for  
30 inhibiting the development of a cancer in a patient, comprising administering to a

patient a pharmaceutical composition as recited above. The patient may be afflicted with prostate cancer, in which case the methods provide treatment for the disease, or a patient considered to be at risk for such a disease may be treated prophylactically.

The present invention further provides, within other aspects, methods for  
5 removing tumor cells from a biological sample, comprising contacting a biological sample with T cells that specifically react with a polypeptide of the present invention, wherein the step of contacting is performed under conditions and for a time sufficient to permit the removal of cells expressing the polypeptide from the sample.

Within related aspects, methods are provided for inhibiting the  
10 development of a cancer in a patient, comprising administering to a patient a biological sample treated as described above.

Methods are further provided, within other aspects, for stimulating and/or expanding T cells specific for a polypeptide of the present invention, comprising contacting T cells with one or more of: (i) a polypeptide as described above; (ii) a  
15 polynucleotide encoding such a polypeptide; and (iii) an antigen presenting cell that expresses such a polypeptide; under conditions and for a time sufficient to permit the stimulation and/or expansion of T cells. Isolated T cell populations comprising T cells prepared as described above are also provided.

Within further aspects, the present invention provides methods for  
20 inhibiting the development of a cancer in a patient, comprising administering to a patient an effective amount of a T cell population as described above.

The present invention further provides methods for inhibiting the development of a cancer in a patient, comprising the steps of: (a) incubating CD4<sup>+</sup> and/or CD8<sup>+</sup> T cells isolated from a patient with one or more of: (i) a polypeptide  
25 comprising at least an immunogenic portion of polypeptide disclosed herein; (ii) a polynucleotide encoding such a polypeptide; and (iii) an antigen-presenting cell that expressed such a polypeptide; and (b) administering to the patient an effective amount of the proliferated T cells, thereby inhibiting the development of a cancer in the patient. Proliferated cells may, but need not, be cloned prior to administration to the patient.

Within further aspects, the present invention provides methods for determining the presence or absence of a cancer, preferably a prostate cancer, in a patient comprising: (a) contacting a biological sample obtained from a patient with a binding agent that binds to a polypeptide as recited above; (b) detecting in the sample an amount of polypeptide that binds to the binding agent; and (c) comparing the amount of polypeptide with a predetermined cut-off value, and therefrom determining the presence or absence of a cancer in the patient. Within preferred embodiments, the binding agent is an antibody, more preferably a monoclonal antibody.

The present invention also provides, within other aspects, methods for monitoring the progression of a cancer in a patient. Such methods comprise the steps of: (a) contacting a biological sample obtained from a patient at a first point in time with a binding agent that binds to a polypeptide as recited above; (b) detecting in the sample an amount of polypeptide that binds to the binding agent; (c) repeating steps (a) and (b) using a biological sample obtained from the patient at a subsequent point in time; and (d) comparing the amount of polypeptide detected in step (c) with the amount detected in step (b), and therefrom monitoring the progression of the cancer in the patient.

The present invention further provides, within other aspects, methods for determining the presence or absence of a cancer in a patient, comprising the steps of: (a) contacting a biological sample obtained from a patient with an oligonucleotide that hybridizes to a polynucleotide of the present invention; (b) detecting in the sample a level of a polynucleotide, preferably mRNA, that hybridizes to the oligonucleotide; and (c) comparing the level of polynucleotide that hybridizes to the oligonucleotide with a predetermined cut-off value, and therefrom determining the presence or absence of a cancer in the patient. Within certain embodiments, the amount of mRNA is detected via polymerase chain reaction using, for example, at least one oligonucleotide primer that hybridizes to a polynucleotide of the present invention, or a complement of such a polynucleotide. Within other embodiments, the amount of mRNA is detected using a hybridization technique, employing an oligonucleotide probe that hybridizes to an inventive polynucleotide, or a complement of such a polynucleotide.

In related aspects, methods are provided for monitoring the progression of a cancer in a patient, comprising the steps of: (a) contacting a biological sample obtained from a patient with an oligonucleotide that hybridizes to a polynucleotide of the present invention; (b) detecting in the sample an amount of a polynucleotide that  
5 hybridizes to the oligonucleotide; (c) repeating steps (a) and (b) using a biological sample obtained from the patient at a subsequent point in time; and (d) comparing the amount of polynucleotide detected in step (c) with the amount detected in step (b), and therefrom monitoring the progression of the cancer in the patient.

Within further aspects, the present invention provides antibodies, such as  
10 monoclonal antibodies, that bind to a polypeptide as described above, as well as diagnostic kits comprising such antibodies. Diagnostic kits comprising one or more oligonucleotide probes or primers as described above are also provided.

These and other aspects of the present invention will become apparent upon reference to the following detailed description and attached drawings. All  
15 references disclosed herein are hereby incorporated by reference in their entirety as if each was incorporated individually.

#### BRIEF DESCRIPTION OF THE DRAWINGS AND SEQUENCE IDENTIFIERS

Figure 1 illustrates the ability of T cells to kill fibroblasts expressing the representative prostate-specific polypeptide P502S, as compared to control fibroblasts.  
20 The percentage lysis is shown as a series of effector:target ratios, as indicated.

Figures 2A and 2B illustrate the ability of T cells to recognize cells expressing the representative prostate-specific polypeptide P502S. In each case, the number of  $\gamma$ -interferon spots is shown for different numbers of responders. In Figure 2A, data is presented for fibroblasts pulsed with the P2S-12 peptide, as compared to  
25 fibroblasts pulsed with a control E75 peptide. In Figure 2B, data is presented for fibroblasts expressing P502S, as compared to fibroblasts expressing HER-2/*neu*.

Figure 3 represents a peptide competition binding assay showing that the P1S#10 peptide, derived from P501S, binds HLA-A2. Peptide P1S#10 inhibits HLA-A2 restricted presentation of fluM58 peptide to CTL clone D150M58 in TNF release



bioassay. D150M58 CTL is specific for the HLA-A2 binding influenza matrix peptide fluM58.

Figure 4 illustrates the ability of T cell lines generated from P1S#10 immunized mice to specifically lyse P1S#10-pulsed Jurkat A2Kb targets and P501S-  
5 transduced Jurkat A2Kb targets, as compared to EGFP-transduced Jurkat A2Kb. The percent lysis is shown as a series of effector to target ratios, as indicated.

Figure 5 illustrates the ability of a T cell clone to recognize and specifically lyse Jurkat A2Kb cells expressing the representative prostate-specific polypeptide P501S, thereby demonstrating that the P1S#10 peptide may be a naturally  
10 processed epitope of the P501S polypeptide.

Figures 6A and 6B are graphs illustrating the specificity of a CD8<sup>+</sup> cell line (3A-1) for a representative prostate-specific antigen (P501S). Figure 6A shows the results of a <sup>51</sup>Cr release assay. The percent specific lysis is shown as a series of effector:target ratios, as indicated. Figure 6B shows the production of interferon-  
15 gamma by 3A-1 cells stimulated with autologous B-LCL transduced with P501S, at varying effector:target ratios as indicated.

Figure 7 is a Western blot showing the expression of P501S in baculovirus.

Figure 8 illustrates the results of epitope mapping studies on P501S.

Figure 9 is a schematic representation of the P501S protein showing the  
20 location of transmembrane domains and predicted intracellular and extracellular domains.

Figure 10 is a genomic map showing the location of the prostate genes P775P, P704P, B305D, P712P and P774P within the Cat Eye Syndrome region of  
25 chromosome 22q11.2

Figure 11 shows the results of an ELISA assay to determine the specificity of rabbit polyclonal antisera raised against P501S.

SEQ ID NO: 1 is the determined cDNA sequence for F1-13

SEQ ID NO: 2 is the determined 3' cDNA sequence for F1-12

30 SEQ ID NO: 3 is the determined 5' cDNA sequence for F1-12

SEQ ID NO: 4 is the determined 3' cDNA sequence for F1-16  
SEQ ID NO: 5 is the determined 3' cDNA sequence for H1-1  
SEQ ID NO: 6 is the determined 3' cDNA sequence for H1-9  
SEQ ID NO: 7 is the determined 3' cDNA sequence for H1-4  
5 SEQ ID NO: 8 is the determined 3' cDNA sequence for J1-17  
SEQ ID NO: 9 is the determined 5' cDNA sequence for J1-17  
SEQ ID NO: 10 is the determined 3' cDNA sequence for L1-12  
SEQ ID NO: 11 is the determined 5' cDNA sequence for L1-12  
SEQ ID NO: 12 is the determined 3' cDNA sequence for N1-1862  
10 SEQ ID NO: 13 is the determined 5' cDNA sequence for N1-1862  
SEQ ID NO: 14 is the determined 3' cDNA sequence for J1-13  
SEQ ID NO: 15 is the determined 5' cDNA sequence for J1-13  
SEQ ID NO: 16 is the determined 3' cDNA sequence for J1-19  
SEQ ID NO: 17 is the determined 5' cDNA sequence for J1-19  
15 SEQ ID NO: 18 is the determined 3' cDNA sequence for J1-25  
SEQ ID NO: 19 is the determined 5' cDNA sequence for J1-25  
SEQ ID NO: 20 is the determined 5' cDNA sequence for J1-24  
SEQ ID NO: 21 is the determined 3' cDNA sequence for J1-24  
SEQ ID NO: 22 is the determined 5' cDNA sequence for K1-58  
20 SEQ ID NO: 23 is the determined 3' cDNA sequence for K1-58  
SEQ ID NO: 24 is the determined 5' cDNA sequence for K1-63  
SEQ ID NO: 25 is the determined 3' cDNA sequence for K1-63  
SEQ ID NO: 26 is the determined 5' cDNA sequence for L1-4  
SEQ ID NO: 27 is the determined 3' cDNA sequence for L1-4  
25 SEQ ID NO: 28 is the determined 5' cDNA sequence for L1-14  
SEQ ID NO: 29 is the determined 3' cDNA sequence for L1-14  
SEQ ID NO: 30 is the determined 3' cDNA sequence for J1-12  
SEQ ID NO: 31 is the determined 3' cDNA sequence for J1-16  
SEQ ID NO: 32 is the determined 3' cDNA sequence for J1-21  
30 SEQ ID NO: 33 is the determined 3' cDNA sequence for K1-48

SEQ ID NO: 34 is the determined 3' cDNA sequence for K1-55  
SEQ ID NO: 35 is the determined 3' cDNA sequence for L1-2  
SEQ ID NO: 36 is the determined 3' cDNA sequence for L1-6  
SEQ ID NO: 37 is the determined 3' cDNA sequence for N1-1858  
5 SEQ ID NO: 38 is the determined 3' cDNA sequence for N1-1860  
SEQ ID NO: 39 is the determined 3' cDNA sequence for N1-1861  
SEQ ID NO: 40 is the determined 3' cDNA sequence for N1-1864  
SEQ ID NO: 41 is the determined cDNA sequence for P5  
SEQ ID NO: 42 is the determined cDNA sequence for P8  
10 SEQ ID NO: 43 is the determined cDNA sequence for P9  
SEQ ID NO: 44 is the determined cDNA sequence for P18  
SEQ ID NO: 45 is the determined cDNA sequence for P20  
SEQ ID NO: 46 is the determined cDNA sequence for P29  
SEQ ID NO: 47 is the determined cDNA sequence for P30  
15 SEQ ID NO: 48 is the determined cDNA sequence for P34  
SEQ ID NO: 49 is the determined cDNA sequence for P36  
SEQ ID NO: 50 is the determined cDNA sequence for P38  
SEQ ID NO: 51 is the determined cDNA sequence for P39  
SEQ ID NO: 52 is the determined cDNA sequence for P42  
20 SEQ ID NO: 53 is the determined cDNA sequence for P47  
SEQ ID NO: 54 is the determined cDNA sequence for P49  
SEQ ID NO: 55 is the determined cDNA sequence for P50  
SEQ ID NO: 56 is the determined cDNA sequence for P53  
SEQ ID NO: 57 is the determined cDNA sequence for P55  
25 SEQ ID NO: 58 is the determined cDNA sequence for P60  
SEQ ID NO: 59 is the determined cDNA sequence for P64  
SEQ ID NO: 60 is the determined cDNA sequence for P65  
SEQ ID NO: 61 is the determined cDNA sequence for P73  
SEQ ID NO: 62 is the determined cDNA sequence for P75  
30 SEQ ID NO: 63 is the determined cDNA sequence for P76

SEQ ID NO: 64 is the determined cDNA sequence for P79

SEQ ID NO: 65 is the determined cDNA sequence for P84

SEQ ID NO: 66 is the determined cDNA sequence for P68

SEQ ID NO: 67 is the determined cDNA sequence for P80 (also referred

5 to as P704P)

SEQ ID NO: 68 is the determined cDNA sequence for P82

SEQ ID NO: 69 is the determined cDNA sequence for U1-3064

SEQ ID NO: 70 is the determined cDNA sequence for U1-3065

SEQ ID NO: 71 is the determined cDNA sequence for V1-3692

10 SEQ ID NO: 72 is the determined cDNA sequence for 1A-3905

SEQ ID NO: 73 is the determined cDNA sequence for V1-3686

SEQ ID NO: 74 is the determined cDNA sequence for R1-2330

SEQ ID NO: 75 is the determined cDNA sequence for 1B-3976

SEQ ID NO: 76 is the determined cDNA sequence for V1-3679

15 SEQ ID NO: 77 is the determined cDNA sequence for 1G-4736

SEQ ID NO: 78 is the determined cDNA sequence for 1G-4738

SEQ ID NO: 79 is the determined cDNA sequence for 1G-4741

SEQ ID NO: 80 is the determined cDNA sequence for 1G-4744

SEQ ID NO: 81 is the determined cDNA sequence for 1G-4734

20 SEQ ID NO: 82 is the determined cDNA sequence for 1H-4774

SEQ ID NO: 83 is the determined cDNA sequence for 1H-4781

SEQ ID NO: 84 is the determined cDNA sequence for 1H-4785

SEQ ID NO: 85 is the determined cDNA sequence for 1H-4787

SEQ ID NO: 86 is the determined cDNA sequence for 1H-4796

25 SEQ ID NO: 87 is the determined cDNA sequence for 1I-4807

SEQ ID NO: 88 is the determined cDNA sequence for 1I-4810

SEQ ID NO: 89 is the determined cDNA sequence for 1I-4811

SEQ ID NO: 90 is the determined cDNA sequence for 1J-4876

SEQ ID NO: 91 is the determined cDNA sequence for 1K-4884

30 SEQ ID NO: 92 is the determined cDNA sequence for 1K-4896

- SEQ ID NO: 93 is the determined cDNA sequence for 1G-4761  
SEQ ID NO: 94 is the determined cDNA sequence for 1G-4762  
SEQ ID NO: 95 is the determined cDNA sequence for 1H-4766  
SEQ ID NO: 96 is the determined cDNA sequence for 1H-4770  
5 SEQ ID NO: 97 is the determined cDNA sequence for 1H-4771  
SEQ ID NO: 98 is the determined cDNA sequence for 1H-4772  
SEQ ID NO: 99 is the determined cDNA sequence for 1D-4297  
SEQ ID NO: 100 is the determined cDNA sequence for 1D-4309  
SEQ ID NO: 101 is the determined cDNA sequence for 1D.1-4278  
10 SEQ ID NO: 102 is the determined cDNA sequence for 1D-4288  
SEQ ID NO: 103 is the determined cDNA sequence for 1D-4283  
SEQ ID NO: 104 is the determined cDNA sequence for 1D-4304  
SEQ ID NO: 105 is the determined cDNA sequence for 1D-4296  
SEQ ID NO: 106 is the determined cDNA sequence for 1D-4280  
15 SEQ ID NO: 107 is the determined full length cDNA sequence for F1-12  
(also referred to as P504S)  
SEQ ID NO: 108 is the predicted amino acid sequence for F1-12  
SEQ ID NO: 109 is the determined full length cDNA sequence for J1-17  
SEQ ID NO: 110 is the determined full length cDNA sequence for L1-12  
20 (also referred to as P501S)  
SEQ ID NO: 111 is the determined full length cDNA sequence for N1-1862 (also referred to as P503S)  
SEQ ID NO: 112 is the predicted amino acid sequence for J1-17  
SEQ ID NO: 113 is the predicted amino acid sequence for L1-12 (also  
25 referred to as P501S)  
SEQ ID NO: 114 is the predicted amino acid sequence for N1-1862 (also referred to as P503S)  
SEQ ID NO: 115 is the determined cDNA sequence for P89  
SEQ ID NO: 116 is the determined cDNA sequence for P90  
30 SEQ ID NO: 117 is the determined cDNA sequence for P92

SEQ ID NO: 118 is the determined cDNA sequence for P95  
SEQ ID NO: 119 is the determined cDNA sequence for P98  
**SEQ ID NO: 120 is the determined cDNA sequence for P102**  
SEQ ID NO: 121 is the determined cDNA sequence for P110  
5 SEQ ID NO: 122 is the determined cDNA sequence for P111  
SEQ ID NO: 123 is the determined cDNA sequence for P114  
SEQ ID NO: 124 is the determined cDNA sequence for P115  
SEQ ID NO: 125 is the determined cDNA sequence for P116  
SEQ ID NO: 126 is the determined cDNA sequence for P124  
10 SEQ ID NO: 127 is the determined cDNA sequence for P126  
SEQ ID NO: 128 is the determined cDNA sequence for P130  
SEQ ID NO: 129 is the determined cDNA sequence for P133  
SEQ ID NO: 130 is the determined cDNA sequence for P138  
SEQ ID NO: 131 is the determined cDNA sequence for P143  
15 SEQ ID NO: 132 is the determined cDNA sequence for P151  
SEQ ID NO: 133 is the determined cDNA sequence for P156  
SEQ ID NO: 134 is the determined cDNA sequence for P157  
SEQ ID NO: 135 is the determined cDNA sequence for P166  
SEQ ID NO: 136 is the determined cDNA sequence for P176  
20 SEQ ID NO: 137 is the determined cDNA sequence for P178  
SEQ ID NO: 138 is the determined cDNA sequence for P179  
SEQ ID NO: 139 is the determined cDNA sequence for P185  
SEQ ID NO: 140 is the determined cDNA sequence for P192  
SEQ ID NO: 141 is the determined cDNA sequence for P201  
25 SEQ ID NO: 142 is the determined cDNA sequence for P204  
SEQ ID NO: 143 is the determined cDNA sequence for P208  
SEQ ID NO: 144 is the determined cDNA sequence for P211  
SEQ ID NO: 145 is the determined cDNA sequence for P213  
SEQ ID NO: 146 is the determined cDNA sequence for P219  
30 SEQ ID NO: 147 is the determined cDNA sequence for P237

SEQ ID NO: 148 is the determined cDNA sequence for P239  
SEQ ID NO: 149 is the determined cDNA sequence for P248  
SEQ ID NO: 150 is the determined cDNA sequence for P251  
SEQ ID NO: 151 is the determined cDNA sequence for P255  
5 SEQ ID NO: 152 is the determined cDNA sequence for P256  
SEQ ID NO: 153 is the determined cDNA sequence for P259  
SEQ ID NO: 154 is the determined cDNA sequence for P260  
SEQ ID NO: 155 is the determined cDNA sequence for P263  
SEQ ID NO: 156 is the determined cDNA sequence for P264  
10 SEQ ID NO: 157 is the determined cDNA sequence for P266  
SEQ ID NO: 158 is the determined cDNA sequence for P270  
SEQ ID NO: 159 is the determined cDNA sequence for P272  
SEQ ID NO: 160 is the determined cDNA sequence for P278  
SEQ ID NO: 161 is the determined cDNA sequence for P105  
15 SEQ ID NO: 162 is the determined cDNA sequence for P107  
SEQ ID NO: 163 is the determined cDNA sequence for P137  
SEQ ID NO: 164 is the determined cDNA sequence for P194  
SEQ ID NO: 165 is the determined cDNA sequence for P195  
SEQ ID NO: 166 is the determined cDNA sequence for P196  
20 SEQ ID NO: 167 is the determined cDNA sequence for P220  
SEQ ID NO: 168 is the determined cDNA sequence for P234  
SEQ ID NO: 169 is the determined cDNA sequence for P235  
SEQ ID NO: 170 is the determined cDNA sequence for P243  
SEQ ID NO: 171 is the determined cDNA sequence for P703P-DE1  
25 SEQ ID NO: 172 is the predicted amino acid sequence for P703P-DE1  
SEQ ID NO: 173 is the determined cDNA sequence for P703P-DE2  
SEQ ID NO: 174 is the determined cDNA sequence for P703P-DE6  
SEQ ID NO: 175 is the determined cDNA sequence for P703P-DE13  
SEQ ID NO: 176 is the predicted amino acid sequence for P703P-DE13  
30 SEQ ID NO: 177 is the determined cDNA sequence for P703P-DE14

SEQ ID NO: 178 is the predicted amino acid sequence for P703P-DE14

SEQ ID NO: 179 is the determined extended cDNA sequence for 1G-

4736

SEQ ID NO: 180 is the determined extended cDNA sequence for 1G-

5 4738

SEQ ID NO: 181 is the determined extended cDNA sequence for 1G-

4741

SEQ ID NO: 182 is the determined extended cDNA sequence for 1G-

4744

10

SEQ ID NO: 183 is the determined extended cDNA sequence for 1H-

4774

SEQ ID NO: 184 is the determined extended cDNA sequence for 1H-

4781

SEQ ID NO: 185 is the determined extended cDNA sequence for 1H-

15 4785

SEQ ID NO: 186 is the determined extended cDNA sequence for 1H-

4787

SEQ ID NO: 187 is the determined extended cDNA sequence for 1H-

4796

20

SEQ ID NO: 188 is the determined extended cDNA sequence for 1I-

4807

SEQ ID NO: 189 is the determined 3' cDNA sequence for 1I-4810

SEQ ID NO: 190 is the determined 3' cDNA sequence for 1I-4811

SEQ ID NO: 191 is the determined extended cDNA sequence for 1J-

25 4876

SEQ ID NO: 192 is the determined extended cDNA sequence for 1K-

4884

SEQ ID NO: 193 is the determined extended cDNA sequence for 1K-

4896



- 4761 SEQ ID NO: 194 is the determined extended cDNA sequence for 1G-
- 4762 SEQ ID NO: 195 is the determined extended cDNA sequence for 1G-
- 5 4766 SEQ ID NO: 196 is the determined extended cDNA sequence for 1H-
- SEQ ID NO: 197 is the determined 3' cDNA sequence for 1H-4770
- SEQ ID NO: 198 is the determined 3' cDNA sequence for 1H-4771
- 10 4772 SEQ ID NO: 199 is the determined extended cDNA sequence for 1H-
- SEQ ID NO: 200 is the determined extended cDNA sequence for 1D-
- 4309 SEQ ID NO: 201 is the determined extended cDNA sequence for 1D.1-
- 4278 SEQ ID NO: 202 is the determined extended cDNA sequence for 1D-
- 15 4288 SEQ ID NO: 203 is the determined extended cDNA sequence for 1D-
- 4283 SEQ ID NO: 204 is the determined extended cDNA sequence for 1D-
- 20 4304 SEQ ID NO: 205 is the determined extended cDNA sequence for 1D-
- 4296 SEQ ID NO: 206 is the determined extended cDNA sequence for 1D-
- 4280
- 25 SEQ ID NO: 207 is the determined cDNA sequence for 10-d8fwd
- SEQ ID NO: 208 is the determined cDNA sequence for 10-H10con
- SEQ ID NO: 209 is the determined cDNA sequence for 11-C8rev
- SEQ ID NO: 210 is the determined cDNA sequence for 7.g6fwd
- SEQ ID NO: 211 is the determined cDNA sequence for 7.g6rev
- 30 SEQ ID NO: 212 is the determined cDNA sequence for 8-b5fwd

SEQ ID NO: 213 is the determined cDNA sequence for 8-b5rev  
SEQ ID NO: 214 is the determined cDNA sequence for 8-b6fwd  
SEQ ID NO: 215 is the determined cDNA sequence for 8-b6 rev  
SEQ ID NO: 216 is the determined cDNA sequence for 8-d4fwd  
5 SEQ ID NO: 217 is the determined cDNA sequence for 8-d9rev  
SEQ ID NO: 218 is the determined cDNA sequence for 8-g3fwd  
SEQ ID NO: 219 is the determined cDNA sequence for 8-g3rev  
SEQ ID NO: 220 is the determined cDNA sequence for 8-h11rev  
SEQ ID NO: 221 is the determined cDNA sequence for g-f12fwd  
10 SEQ ID NO: 222 is the determined cDNA sequence for g-f3rev  
SEQ ID NO: 223 is the determined cDNA sequence for P509S  
SEQ ID NO: 224 is the determined cDNA sequence for P510S  
SEQ ID NO: 225 is the determined cDNA sequence for P703DE5  
SEQ ID NO: 226 is the determined cDNA sequence for 9-A11  
15 SEQ ID NO: 227 is the determined cDNA sequence for 8-C6  
SEQ ID NO: 228 is the determined cDNA sequence for 8-H7  
SEQ ID NO: 229 is the determined cDNA sequence for JPTPN13  
SEQ ID NO: 230 is the determined cDNA sequence for JPTPN14  
SEQ ID NO: 231 is the determined cDNA sequence for JPTPN23  
20 SEQ ID NO: 232 is the determined cDNA sequence for JPTPN24  
SEQ ID NO: 233 is the determined cDNA sequence for JPTPN25  
SEQ ID NO: 234 is the determined cDNA sequence for JPTPN30  
SEQ ID NO: 235 is the determined cDNA sequence for JPTPN34  
SEQ ID NO: 236 is the determined cDNA sequence for PTPN35  
25 SEQ ID NO: 237 is the determined cDNA sequence for JPTPN36  
SEQ ID NO: 238 is the determined cDNA sequence for JPTPN38  
SEQ ID NO: 239 is the determined cDNA sequence for JPTPN39  
SEQ ID NO: 240 is the determined cDNA sequence for JPTPN40  
SEQ ID NO: 241 is the determined cDNA sequence for JPTPN41  
30 SEQ ID NO: 242 is the determined cDNA sequence for JPTPN42

SEQ ID NO: 243 is the determined cDNA sequence for JPTPN45  
SEQ ID NO: 244 is the determined cDNA sequence for JPTPN46  
SEQ ID NO: 245 is the determined cDNA sequence for JPTPN51  
SEQ ID NO: 246 is the determined cDNA sequence for JPTPN56  
5 SEQ ID NO: 247 is the determined cDNA sequence for PTPN64  
SEQ ID NO: 248 is the determined cDNA sequence for JPTPN65  
SEQ ID NO: 249 is the determined cDNA sequence for JPTPN67  
SEQ ID NO: 250 is the determined cDNA sequence for JPTPN76  
SEQ ID NO: 251 is the determined cDNA sequence for JPTPN84  
10 SEQ ID NO: 252 is the determined cDNA sequence for JPTPN85  
SEQ ID NO: 253 is the determined cDNA sequence for JPTPN86  
SEQ ID NO: 254 is the determined cDNA sequence for JPTPN87  
SEQ ID NO: 255 is the determined cDNA sequence for JPTPN88  
SEQ ID NO: 256 is the determined cDNA sequence for JP1F1  
15 SEQ ID NO: 257 is the determined cDNA sequence for JP1F2  
SEQ ID NO: 258 is the determined cDNA sequence for JP1C2  
SEQ ID NO: 259 is the determined cDNA sequence for JP1B1  
SEQ ID NO: 260 is the determined cDNA sequence for JP1B2  
SEQ ID NO: 261 is the determined cDNA sequence for JP1D3  
20 SEQ ID NO: 262 is the determined cDNA sequence for JP1A4  
SEQ ID NO: 263 is the determined cDNA sequence for JP1F5  
SEQ ID NO: 264 is the determined cDNA sequence for JP1E6  
SEQ ID NO: 265 is the determined cDNA sequence for JP1D6  
SEQ ID NO: 266 is the determined cDNA sequence for JP1B5  
25 SEQ ID NO: 267 is the determined cDNA sequence for JP1A6  
SEQ ID NO: 268 is the determined cDNA sequence for JP1E8  
SEQ ID NO: 269 is the determined cDNA sequence for JP1D7  
SEQ ID NO: 270 is the determined cDNA sequence for JP1D9  
SEQ ID NO: 271 is the determined cDNA sequence for JP1C10  
30 SEQ ID NO: 272 is the determined cDNA sequence for JP1A9

SEQ ID NO: 273 is the determined cDNA sequence for JP1F12  
SEQ ID NO: 274 is the determined cDNA sequence for JP1E12  
SEQ ID NO: 275 is the determined cDNA sequence for JP1D11  
SEQ ID NO: 276 is the determined cDNA sequence for JP1C11  
5 SEQ ID NO: 277 is the determined cDNA sequence for JP1C12  
SEQ ID NO: 278 is the determined cDNA sequence for JP1B12  
SEQ ID NO: 279 is the determined cDNA sequence for JP1A12  
SEQ ID NO: 280 is the determined cDNA sequence for JP8G2  
SEQ ID NO: 281 is the determined cDNA sequence for JP8H1  
10 SEQ ID NO: 282 is the determined cDNA sequence for JP8H2  
SEQ ID NO: 283 is the determined cDNA sequence for JP8A3  
SEQ ID NO: 284 is the determined cDNA sequence for JP8A4  
SEQ ID NO: 285 is the determined cDNA sequence for JP8C3  
SEQ ID NO: 286 is the determined cDNA sequence for JP8G4  
15 SEQ ID NO: 287 is the determined cDNA sequence for JP8B6  
SEQ ID NO: 288 is the determined cDNA sequence for JP8D6  
SEQ ID NO: 289 is the determined cDNA sequence for JP8F5  
SEQ ID NO: 290 is the determined cDNA sequence for JP8A8  
SEQ ID NO: 291 is the determined cDNA sequence for JP8C7  
20 SEQ ID NO: 292 is the determined cDNA sequence for JP8D7  
SEQ ID NO: 293 is the determined cDNA sequence for P8D8  
SEQ ID NO: 294 is the determined cDNA sequence for JP8E7  
SEQ ID NO: 295 is the determined cDNA sequence for JP8F8  
SEQ ID NO: 296 is the determined cDNA sequence for JP8G8  
25 SEQ ID NO: 297 is the determined cDNA sequence for JP8B10  
SEQ ID NO: 298 is the determined cDNA sequence for JP8C10  
SEQ ID NO: 299 is the determined cDNA sequence for JP8E9  
SEQ ID NO: 300 is the determined cDNA sequence for JP8E10  
SEQ ID NO: 301 is the determined cDNA sequence for JP8F9  
30 SEQ ID NO: 302 is the determined cDNA sequence for JP8H9

- SEQ ID NO: 303 is the determined cDNA sequence for JP8C12  
SEQ ID NO: 304 is the determined cDNA sequence for JP8E11  
SEQ ID NO: 305 is the determined cDNA sequence for JP8E12  
SEQ ID NO: 306 is the amino acid sequence for the peptide PS2#12  
5 SEQ ID NO: 307 is the determined cDNA sequence for P711P  
SEQ ID NO: 308 is the determined cDNA sequence for P712P  
SEQ ID NO: 309 is the determined cDNA sequence for CLONE23  
SEQ ID NO: 310 is the determined cDNA sequence for P774P  
SEQ ID NO: 311 is the determined cDNA sequence for P775P  
10 SEQ ID NO: 312 is the determined cDNA sequence for P715P  
SEQ ID NO: 313 is the determined cDNA sequence for P710P  
SEQ ID NO: 314 is the determined cDNA sequence for P767P  
SEQ ID NO: 315 is the determined cDNA sequence for P768P  
SEQ ID NO: 316-325 are the determined cDNA sequences of previously  
15 isolated genes  
SEQ ID NO: 326 is the determined cDNA sequence for P703PDE5  
SEQ ID NO: 327 is the predicted amino acid sequence for P703PDE5  
SEQ ID NO: 328 is the determined cDNA sequence for P703P6.26  
SEQ ID NO: 329 is the predicted amino acid sequence for P703P6.26  
20 SEQ ID NO: 330 is the determined cDNA sequence for P703PX-23  
SEQ ID NO: 331 is the predicted amino acid sequence for P703PX-23  
SEQ ID NO: 332 is the determined full length cDNA sequence for  
P509S  
SEQ ID NO: 333 is the determined extended cDNA sequence for P707P  
25 (also referred to as 11-C9)  
SEQ ID NO: 334 is the determined cDNA sequence for P714P  
SEQ ID NO: 335 is the determined cDNA sequence for P705P (also  
referred to as 9-F3)  
SEQ ID NO: 336 is the predicted amino acid sequence for P705P  
30 SEQ ID NO: 337 is the amino acid sequence of the peptide P1S#10

- SEQ ID NO: 338 is the amino acid sequence of the peptide p5
- SEQ ID NO: 339 is the predicted amino acid sequence of P509S
- SEQ ID NO: 340 is the determined cDNA sequence for P778P**
- SEQ ID NO: 341 is the determined cDNA sequence for P786P
- 5 SEQ ID NO: 342 is the determined cDNA sequence for P789P
- SEQ ID NO: 343 is the determined cDNA sequence for a clone showing  
homology to Homo sapiens MM46 mRNA
- SEQ ID NO: 344 is the determined cDNA sequence for a clone showing  
homology to Homo sapiens TNF-alpha stimulated ABC protein (ABC50) mRNA
- 10 SEQ ID NO: 345 is the determined cDNA sequence for a clone showing  
homology to Homo sapiens mRNA for E-cadherin
- SEQ ID NO: 346 is the determined cDNA sequence for a clone showing  
homology to Human nuclear-encoded mitochondrial serine hydroxymethyltransferase  
(SHMT)
- 15 SEQ ID NO: 347 is the determined cDNA sequence for a clone showing  
homology to Homo sapiens natural resistance-associated macrophage protein2  
(NRAMP2)
- SEQ ID NO: 348 is the determined cDNA sequence for a clone showing  
homology to Homo sapiens phosphoglucosyltransferase-related protein (PGMRP)
- 20 SEQ ID NO: 349 is the determined cDNA sequence for a clone showing  
homology to Human mRNA for proteasome subunit p40
- SEQ ID NO: 350 is the determined cDNA sequence for P777P
- SEQ ID NO: 351 is the determined cDNA sequence for P779P
- SEQ ID NO: 352 is the determined cDNA sequence for P790P
- 25 SEQ ID NO: 353 is the determined cDNA sequence for P784P
- SEQ ID NO: 354 is the determined cDNA sequence for P776P
- SEQ ID NO: 355 is the determined cDNA sequence for P780P
- SEQ ID NO: 356 is the determined cDNA sequence for P544S
- SEQ ID NO: 357 is the determined cDNA sequence for P745S
- 30 SEQ ID NO: 358 is the determined cDNA sequence for P782P

- SEQ ID NO: 359 is the determined cDNA sequence for P783P
- SEQ ID NO: 360 is the determined cDNA sequence for unknown 17984
- SEQ ID NO: 361 is the determined cDNA sequence for P787P
- SEQ ID NO: 362 is the determined cDNA sequence for P788P
- 5 SEQ ID NO: 363 is the determined cDNA sequence for unknown 17994
- SEQ ID NO: 364 is the determined cDNA sequence for P781P
- SEQ ID NO: 365 is the determined cDNA sequence for P785P
- SEQ ID NO: 366-375 are the determined cDNA sequences for splice variants of B305D.
- 10 SEQ ID NO: 376 is the predicted amino acid sequence encoded by the sequence of SEQ ID NO: 366.
- SEQ ID NO: 377 is the predicted amino acid sequence encoded by the sequence of SEQ ID NO: 372.
- SEQ ID NO: 378 is the predicted amino acid sequence encoded by the sequence of SEQ ID NO: 373.
- 15 SEQ ID NO: 379 is the predicted amino acid sequence encoded by the sequence of SEQ ID NO: 374.
- SEQ ID NO: 380 is the predicted amino acid sequence encoded by the sequence of SEQ ID NO: 375.
- 20 SEQ ID NO: 381 is the determined cDNA sequence for B716P.
- SEQ ID NO: 382 is the determined full-length cDNA sequence for P711P.
- SEQ ID NO: 383 is the predicted amino acid sequence for P711P.
- SEQ ID NO: 384 is the cDNA sequence for P1000C.
- 25 SEQ ID NO: 385 is the cDNA sequence for CGI-82.
- SEQ ID NO: 386 is the cDNA sequence for 23320.
- SEQ ID NO: 387 is the cDNA sequence for CGI-69.
- SEQ ID NO: 388 is the cDNA sequence for L-idoitol-2-dehydrogenase.
- SEQ ID NO: 389 is the cDNA sequence for 23379.
- 30 SEQ ID NO: 390 is the cDNA sequence for 23381.

- SEQ ID NO:391 is the cDNA sequence for KIAA0122.  
SEQ ID NO:392 is the cDNA sequence for 23399.  
SEQ ID NO:393 is the cDNA sequence for a previously identified gene.  
SEQ ID NO:394 is the cDNA sequence for HCLBP.  
5 SEQ ID NO:395 is the cDNA sequence for transglutaminase.  
SEQ ID NO:396 is the cDNA sequence for a previously identified gene.  
SEQ ID NO:397 is the cDNA sequence for PAP.  
SEQ ID NO:398 is the cDNA sequence for Ets transcription factor  
PDEF.  
10 SEQ ID NO:399 is the cDNA sequence for hTGR.  
SEQ ID NO:400 is the cDNA sequence for KIAA0295.  
SEQ ID NO:401 is the cDNA sequence for 22545.  
SEQ ID NO:402 is the cDNA sequence for 22547.  
SEQ ID NO:403 is the cDNA sequence for 22548.  
15 SEQ ID NO:404 is the cDNA sequence for 22550.  
SEQ ID NO:405 is the cDNA sequence for 22551.  
SEQ ID NO:406 is the cDNA sequence for 22552.  
SEQ ID NO:407 is the cDNA sequence for 22553 (also known as  
P1020C).  
20 SEQ ID NO:408 is the cDNA sequence for 22558.  
SEQ ID NO:409 is the cDNA sequence for 22562.  
SEQ ID NO:410 is the cDNA sequence for 22565.  
SEQ ID NO:411 is the cDNA sequence for 22567.  
SEQ ID NO:412 is the cDNA sequence for 22568.  
25 SEQ ID NO:413 is the cDNA sequence for 22570.  
SEQ ID NO:414 is the cDNA sequence for 22571.  
SEQ ID NO:415 is the cDNA sequence for 22572.  
SEQ ID NO:416 is the cDNA sequence for 22573.  
SEQ ID NO:417 is the cDNA sequence for 22573.  
30 SEQ ID NO:418 is the cDNA sequence for 22575.



SEQ ID NO:419 is the cDNA sequence for 22580.  
SEQ ID NO:420 is the cDNA sequence for 22581.  
SEQ ID NO:421 is the cDNA sequence for 22582.  
SEQ ID NO:422 is the cDNA sequence for 22583.  
5 SEQ ID NO:423 is the cDNA sequence for 22584.  
SEQ ID NO:424 is the cDNA sequence for 22585.  
SEQ ID NO:425 is the cDNA sequence for 22586.  
SEQ ID NO:426 is the cDNA sequence for 22587.  
SEQ ID NO:427 is the cDNA sequence for 22588.  
10 SEQ ID NO:428 is the cDNA sequence for 22589.  
SEQ ID NO:429 is the cDNA sequence for 22590.  
SEQ ID NO:430 is the cDNA sequence for 22591.  
SEQ ID NO:431 is the cDNA sequence for 22592.  
SEQ ID NO:432 is the cDNA sequence for 22593.  
15 SEQ ID NO:433 is the cDNA sequence for 22594.  
SEQ ID NO:434 is the cDNA sequence for 22595.  
SEQ ID NO:435 is the cDNA sequence for 22596.  
SEQ ID NO:436 is the cDNA sequence for 22847.  
SEQ ID NO:437 is the cDNA sequence for 22848.  
20 SEQ ID NO:438 is the cDNA sequence for 22849.  
SEQ ID NO:439 is the cDNA sequence for 22851.  
SEQ ID NO:440 is the cDNA sequence for 22852.  
SEQ ID NO:441 is the cDNA sequence for 22853.  
SEQ ID NO:442 is the cDNA sequence for 22854.  
25 SEQ ID NO:443 is the cDNA sequence for 22855.  
SEQ ID NO:444 is the cDNA sequence for 22856.  
SEQ ID NO:445 is the cDNA sequence for 22857.  
SEQ ID NO:446 is the cDNA sequence for 23601.  
SEQ ID NO:447 is the cDNA sequence for 23602.  
30 SEQ ID NO:448 is the cDNA sequence for 23605.

- SEQ ID NO:449 is the cDNA sequence for 23606.
- SEQ ID NO:450 is the cDNA sequence for 23612.
- SEQ ID NO:451 is the cDNA sequence for 23614.
- SEQ ID NO:452 is the cDNA sequence for 23618.
- 5 SEQ ID NO:453 is the cDNA sequence for 23622.
- SEQ ID NO:454 is the cDNA sequence for folate hydrolase.
- SEQ ID NO:455 is the cDNA sequence for LIM protein.
- SEQ ID NO:456 is the cDNA sequence for a known gene.
- SEQ ID NO:457 is the cDNA sequence for a known gene.
- 10 SEQ ID NO:458 is the cDNA sequence for a previously identified gene.
- SEQ ID NO:459 is the cDNA sequence for 23045.
- SEQ ID NO:460 is the cDNA sequence for 23032.
- SEQ ID NO:461 is the cDNA sequence for clone 23054.
- SEQ ID NO:462-467 are cDNA sequences for known genes.
- 15 SEQ ID NO:468-471 are cDNA sequences for P710P.
- SEQ ID NO:472 is a cDNA sequence for P1001C.
- SEQ ID NO: 473 is the determined cDNA sequence for a first splice variant of P775P (referred to as 27505).
- SEQ ID NO: 474 is the determined cDNA sequence for a second splice variant of P775P (referred to as 19947).
- 20 SEQ ID NO: 475 is the determined cDNA sequence for a third splice variant of P775P (referred to as 19941).
- SEQ ID NO: 476 is the determined cDNA sequence for a fourth splice variant of P775P (referred to as 19937).
- 25 SEQ ID NO: 477 is a first predicted amino acid sequence encoded by the sequence of SEQ ID NO: 474.
- SEQ ID NO: 478 is a second predicted amino acid sequence encoded by the sequence of SEQ ID NO: 474.
- SEQ ID NO: 479 is the predicted amino acid sequence encoded by the sequence of SEQ ID NO: 475.
- 30

SEQ ID NO: 480 is a first predicted amino acid sequence encoded by the sequence of SEQ ID NO: 473.

SEQ ID NO: 481 is a second predicted amino acid sequence encoded by the sequence of SEQ ID NO: 473.

5       SEQ ID NO: 482 is a third predicted amino acid sequence encoded by the sequence of SEQ ID NO: 473.

SEQ ID NO: 483 is a fourth predicted amino acid sequence encoded by the sequence of SEQ ID NO: 473.

10       SEQ ID NO: 484 is the first 30 amino acids of the *M. tuberculosis* antigen Ra12.

SEQ ID NO: 485 is the PCR primer AW025.

SEQ ID NO: 486 is the PCR primer AW003.

SEQ ID NO: 487 is the PCR primer AW027.

SEQ ID NO: 488 is the PCR primer AW026.

15       SEQ ID NO: 489-501 are peptides employed in epitope mapping studies.

SEQ ID NO: 502 is the determined cDNA sequence of the complementarity determining region for the anti-P503S monoclonal antibody 20D4.

SEQ ID NO: 503 is the determined cDNA sequence of the complementarity determining region for the anti-P503S monoclonal antibody JA1.

20       SEQ ID NO: 504 & 505 are peptides employed in epitope mapping studies.

SEQ ID NO: 506 is the determined cDNA sequence of the complementarity determining region for the anti-P703P monoclonal antibody 8H2.

25       SEQ ID NO: 507 is the determined cDNA sequence of the complementarity determining region for the anti-P703P monoclonal antibody 7H8.

SEQ ID NO: 508 is the determined cDNA sequence of the complementarity determining region for the anti-P703P monoclonal antibody 2D4.

SEQ ID NO: 509-522 are peptides employed in epitope mapping studies.

30       SEQ ID NO: 523 is a mature form of P703P used to raise antibodies against P703P.

SEQ ID NO: 524 is the putative full-length cDNA sequence of P703P.

SEQ ID NO: 525 is the predicted amino acid sequence encoded by SEQ ID NO: 524.

SEQ ID NO: 526 is the full-length cDNA sequence for P790P.

5 SEQ ID NO: 527 is the predicted amino acid sequence for P790P.

SEQ ID NO: 528 & 529 are PCR primers.

SEQ ID NO: 530 is the cDNA sequence of a splice variant of SEQ ID NO: 366.

10 SEQ ID NO: 531 is the cDNA sequence of the open reading frame of SEQ ID NO: 530.

SEQ ID NO: 532 is the predicted amino acid encoded by the sequence of SEQ ID NO: 531.

SEQ ID NO: 533 is the DNA sequence of a putative ORF of P775P.

15 SEQ ID NO: 534 is the predicted amino acid sequence encoded by SEQ ID NO: 533.

SEQ ID NO: 535 is a first full-length cDNA sequence for P510S.

SEQ ID NO: 536 is a second full-length cDNA sequence for P510S.

SEQ ID NO: 537 is the predicted amino acid sequence encoded by SEQ ID NO: 535.

20 SEQ ID NO: 538 is the predicted amino acid sequence encoded by SEQ ID NO: 536.

SEQ ID NO: 539 is the peptide P501S-370.

SEQ ID NO: 540 is the peptide P501S-376.

SEQ ID NO: 541-551 are epitopes of P501S.

25 SEQ ID NO: 552 is an extended cDNA sequence for P712P.

SEQ ID NO: 553-568 are the amino acid sequences encoded by predicted open reading frames within SEQ ID NO: 552.

SEQ ID NO: 569 is an extended cDNA sequence for P776P.

30 SEQ ID NO: 570 is the determined cDNA sequence for a splice variant of P776P referred to as contig 6.

SEQ ID NO: 571 is the determined cDNA sequence for a splice variant of P776P referred to as contig 7.

SEQ ID NO: 572 is the determined cDNA sequence for a splice variant of P776P referred to as contig 14.

5           SEQ ID NO: 573 is the amino acid sequence encoded by a first predicted ORF of SEQ ID NO: 570.

SEQ ID NO: 574 is the amino acid sequence encoded by a second predicted ORF of SEQ ID NO: 570.

10          SEQ ID NO: 575 is the amino acid sequence encoded by a predicted ORF of SEQ ID NO: 571.

SEQ ID NO: 576-586 are amino acid sequences encoded by predicted ORFs of SEQ ID NO: 569.

SEQ ID NO: 587 is a DNA consensus sequence of the sequences of P767P and P777P.

15          SEQ ID NO: 588-590 are amino acid sequences encoded by predicted ORFs of SEQ ID NO: 587.

SEQ ID NO: 591 is an extended cDNA sequence for P1020C.

SEQ ID NO: 592 is the predicted amino acid sequence encoded by the sequence of SEQ ID NO: P1020C.

20          SEQ ID NO: 593 is a splice variant of P775P referred to as 50748.

SEQ ID NO: 594 is a splice variant of P775P referred to as 50717.

SEQ ID NO: 595 is a splice variant of P775P referred to as 45985.

SEQ ID NO: 596 is a splice variant of P775P referred to as 38769.

SEQ ID NO: 597 is a splice variant of P775P referred to as 37922.

25          SEQ ID NO: 598 is a splice variant of P510S referred to as 49274.

SEQ ID NO: 599 is a splice variant of P510S referred to as 39487.

SEQ ID NO: 600 is a splice variant of P504S referred to as 5167.16.

SEQ ID NO: 601 is a splice variant of P504S referred to as 5167.1.

SEQ ID NO: 602 is a splice variant of P504S referred to as 5163.46.

30          SEQ ID NO: 603 is a splice variant of P504S referred to as 5163.42.

SEQ ID NO: 604 is a splice variant of P504S referred to as 5163.34.

SEQ ID NO: 605 is a splice variant of P504S referred to as 5163.17.

**SEQ ID NO: 606 is a splice variant of P501S referred to as 10640.**

SEQ ID NO: 607-615 are the sequences of PCR primers.

5           SEQ ID NO: 616 is the determined cDNA sequence of a fusion of P703P  
and PSA.

SEQ ID NO: 617 is the amino acid sequence of the fusion of P703P and  
PSA.

SEQ ID NO: 618 is the cDNA sequence of the gene DD3.

10           SEQ ID NO: 619 is an extended cDNA sequence for P714P.

SEQ ID NO: 620-622 are the cDNA sequences for splice variants of  
P704P.

SEQ ID NO: 623 is the cDNA sequence of a splice variant of P553S  
referred to as P553S-14.

15           SEQ ID NO: 624 is the cDNA sequence of a splice variant of P553S  
referred to as P553S-12.

SEQ ID NO: 625 is the cDNA sequence of a splice variant of P553S  
referred to as P553S-10.

20           SEQ ID NO: 626 is the cDNA sequence of a splice variant of P553S  
referred to as P553S-6.

SEQ ID NO: 627 is the amino acid sequence encoded by SEQ ID NO:  
626.

SEQ ID NO: 628 is a first amino acid sequence encoded by SEQ ID NO:  
623.

25           SEQ ID NO: 629 is a second amino acid sequence encoded by SEQ ID  
NO: 623.

SEQ ID NO: 630 is a first full-length cDNA sequence for prostate-  
specific transglutaminase gene (also referred to herein as P558S).

30           SEQ ID NO: 631 is a second full-length cDNA sequence for prostate-  
specific transglutaminase gene.

SEQ ID NO: 632 is the amino acid sequence encoded by the sequence of SEQ ID NO: 630.

SEQ ID NO: 633 is the amino acid sequence encoded by the sequence of SEQ ID NO: 631.

5 SEQ ID NO: 634 is the full-length cDNA sequence for P788P.

SEQ ID NO: 635 is the amino acid sequence encoded by SEQ ID NO: 634.

SEQ ID NO: 636 is the determined cDNA sequence for a polymorphic variant of P788P.

10 SEQ ID NO: 637 is the amino acid sequence encoded by SEQ ID NO: 636.

SEQ ID NO: 638 is the amino acid sequence of peptide 4 from P703P.

SEQ ID NO: 639 is the cDNA sequence that encodes peptide 4 from P703P.

15 SEQ ID NO: 640-655 are cDNA sequences encoding epitopes of P703P.

SEQ ID NO: 656-671 are the amino acid sequences of epitopes of P703P.

SEQ ID NO: 672 and 673 are PCR primers.

20 SEQ ID NO: 674 is the cDNA sequence encoding an N-terminal portion of P788P expressed in *E. coli*.

SEQ ID NO: 675 is the amino acid sequence of the N-terminal portion of P788P expressed in *E. coli*.

SEQ ID NO: 676 is the amino acid sequence of the *M. tuberculosis* antigen Ra12.

25 SEQ ID NO: 677 and 678 are PCR primers.

SEQ ID NO: 679 is the cDNA sequence for the Ra12-P510S-C construct.

SEQ ID NO: 680 is the cDNA sequence for the P510S-C construct.

SEQ ID NO: 681 is the cDNA sequence for the P510S-E3 construct.

SEQ ID NO: 682 is the amino acid sequence for the Ra12-P510S-C construct.

SEQ ID NO: 683 is the amino acid sequence for the P510S-C construct.

SEQ ID NO: 684 is the amino acid sequence for the P510S-E3 construct.

5 SEQ ID NO: 685-690 are PCR primers.

SEQ ID NO: 691 is the cDNA sequence of the construct Ra12-P775P-ORF3.

SEQ ID NO: 692 is the amino acid sequence of the construct Ra12-P775P-ORF3.

10 SEQ ID NO: 693 and 694 are PCR primers.

SEQ ID NO: 695 is the determined amino acid sequence for a P703P His tag fusion protein.

SEQ ID NO: 696 is the determined cDNA sequence for a P703P His tag fusion protein.

15 SEQ ID NO: 697 and 698 are PCR primers.

SEQ ID NO: 699 is the determined amino acid sequence for a P705P His tag fusion protein.

SEQ ID NO: 700 is the determined cDNA sequence for a P705P His tag fusion protein.

20 SEQ ID NO: 701 and 702 are PCR primers.

SEQ ID NO: 703 is the determined amino acid sequence for a P711P His tag fusion protein.

SEQ ID NO: 704 is the determined cDNA sequence for a P711P His tag fusion protein.

25 SEQ ID NO: 705 is the amino acid sequence of the *M. tuberculosis* antigen Ra12.

SEQ ID NO: 706 and 707 are PCR primers.

SEQ ID NO: 708 is the determined cDNA sequence for the construct Ra12-P501S-E2.



SEQ ID NO: 709 is the determined amino acid sequence for the construct Ra12-P501S-E2.

SEQ ID NO: 710 is the amino acid sequence for an epitope of P501S.

SEQ ID NO: 711 is the DNA sequence encoding SEQ ID NO: 710.

5 SEQ ID NO: 712 is the amino acid sequence for an epitope of P501S.

SEQ ID NO: 713 is the DNA sequence encoding SEQ ID NO: 712.

SEQ ID NO: 714 is a peptide employed in epitope mapping studies.

SEQ ID NO: 715 is the amino acid sequence for an epitope of P501S.

SEQ ID NO: 716 is the DNA sequence encoding SEQ ID NO: 715.

10 SEQ ID NO: 717-719 are the amino acid sequences for CD4 epitopes of P501S.

SEQ ID NO: 720-722 are the DNA sequences encoding the sequences of SEQ ID NO: 717-719.

15 SEQ ID NO: 723-734 are the amino acid sequences for putative CTL epitopes of P703P.

SEQ ID NO: 735 is the full-length cDNA sequence for P789P.

SEQ ID NO: 736 is the amino acid sequence encoded by SEQ ID NO: 735.

20 SEQ ID NO: 737 is the determined full-length cDNA sequence for the splice variant of P776P referred to as contig 6.

SEQ ID NO: 738-739 are determined full-length cDNA sequences for the splice variant of P776P referred to as contig 7.

SEQ ID NO: 740-744 are amino acid sequences encoded by SEQ ID NO: 737.

25 SEQ ID NO: 745-750 are amino acid sequences encoded by the splice variant of P776P referred to as contig 7.

SEQ ID NO: 751 is the full-length cDNA sequence for human transmembrane protease serine 2.

30 SEQ ID NO: 752 is the amino acid sequence encoded by SEQ ID NO: 751.

SEQ ID NO: 753 is the cDNA sequence encoding the first 209 amino acids of human transmembrane protease serine 2.

SEQ ID NO: 754 is the first 209 amino acids of human transmembrane protease serine 2.

5                   SEQ ID NO: 755 is the amino acid sequence of peptide 296-322 of P501S.

SEQ ID NO: 756-759 are PCR primers.

SEQ ID NO: 760 is the determined cDNA sequence of the Vb chain of a T cell receptor for the P501S-specific T cell clone 4E5.

10                   SEQ ID NO: 761 is the determined cDNA sequence of the Va chain of a T cell receptor for the P501S-specific T cell clone 4E5.

SEQ ID NO: 762 is the amino acid sequence encoded by SEQ ID NO 760.

15                   SEQ ID NO: 763 is the amino acid sequence encoded by SEQ ID NO 761.

SEQ ID NO: 764 is the full-length open reading frame for P768P including stop codon.

SEQ ID NO: 765 is the full-length open reading frame for P768P without stop codon.

20                   SEQ ID NO: 766 is the amino acid sequence encoded by SEQ ID NO: 765.

SEQ ID NO: 767-772 are the amino acid sequences for predicted domains of P768P.

SEQ ID NO: 773 is the full-length cDNA sequence of P835P.

25                   SEQ ID NO: 774 is the cDNA sequence of the previously identified clone FLJ13581.

SEQ ID NO: 775 is the cDNA sequence of the open reading frame for P835P with stop codon.

30                   SEQ ID NO: 776 is the cDNA sequence of the open reading frame for P835P without stop codon.

SEQ ID NO: 777 is the full-length amino acid sequence for P835P.

SEQ ID NO: 778-785 are the amino acid sequences of extracellular and intracellular domains of P835P.

SEQ ID NO: 786 is the full-length cDNA sequence for P1000C.

5 SEQ ID NO: 787 is the cDNA sequence of the open reading frame for P1000C, including stop codon.

SEQ ID NO: 788 is the cDNA sequence of the open reading frame for P1000C, without stop codon.

SEQ ID NO: 789 is the full-length amino acid sequence for P1000C.

10 SEQ ID NO: 790 is amino acids 1-100 of SEQ ID NO: 789.

SEQ ID NO: 791 is amino acids 100-492 of SEQ ID NO: 789.

SEQ ID NO: 792 is the amino acid sequence of an  $\alpha$  prepro-P501S recombinant protein.

## 15 DETAILED DESCRIPTION OF THE INVENTION

The present invention is directed generally to compositions and their use in the therapy and diagnosis of cancer, particularly prostate cancer. As described further below, illustrative compositions of the present invention include, but are not restricted to, polypeptides, particularly immunogenic polypeptides, polynucleotides encoding such polypeptides, antibodies and other binding agents, antigen presenting cells (APCs) and immune system cells (*e.g.*, T cells).

The practice of the present invention will employ, unless indicated specifically to the contrary, conventional methods of virology, immunology, microbiology, molecular biology and recombinant DNA techniques within the skill of the art, many of which are described below for the purpose of illustration. Such techniques are explained fully in the literature. See, *e.g.*, Sambrook, et al. Molecular Cloning: A Laboratory Manual (2nd Edition, 1989); Maniatis et al. Molecular Cloning: A Laboratory Manual (1982); DNA Cloning: A Practical Approach, vol. I & II (D. Glover, ed.); Oligonucleotide Synthesis (N. Gait, ed., 1984); Nucleic Acid

Hybridization (B. Hames & S. Higgins, eds., 1985); Transcription and Translation (B. Hames & S. Higgins, eds., 1984); Animal Cell Culture (R. Freshney, ed., 1986); Perbal, A Practical Guide to Molecular Cloning (1984).

5 All publications, patents and patent applications cited herein, whether supra or infra, are hereby incorporated by reference in their entirety.

As used in this specification and the appended claims, the singular forms "a," "an" and "the" include plural references unless the content clearly dictates otherwise.

#### Polypeptide Compositions

10 As used herein, the term "polypeptide" is used in its conventional meaning, *i.e.*, as a sequence of amino acids. The polypeptides are not limited to a specific length of the product; thus, peptides, oligopeptides, and proteins are included within the definition of polypeptide, and such terms may be used interchangeably herein unless specifically indicated otherwise. This term also does not refer to or exclude post-  
15 expression modifications of the polypeptide, for example, glycosylations, acetylations, phosphorylations and the like, as well as other modifications known in the art, both naturally occurring and non-naturally occurring. A polypeptide may be an entire protein, or a subsequence thereof. Particular polypeptides of interest in the context of this invention are amino acid subsequences comprising epitopes, *i.e.*, antigenic  
20 determinants substantially responsible for the immunogenic properties of a polypeptide and being capable of evoking an immune response.

Particularly illustrative polypeptides of the present invention comprise those encoded by a polynucleotide sequence set forth in any one of SEQ ID NOs: 1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382  
25 and 384-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-626, 630, 631, 634, 636, 639-655, 674, 680, 681, 711, 713, 716, 720-722, 735, 737-739, 751, 753, 764, 765, 773-776 and 786-788, or a sequence that hybridizes under moderately stringent conditions, or, alternatively, under highly stringent conditions, to a polynucleotide sequence set forth in any one of SEQ ID NOs: 1-111, 115-171, 173-175,

177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 and 384-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-626, 630, 631, 634, 636, 639-655, 674, 680, 681, 711, 713, 716, 720-722, 735, 737-739, 751, 753, 764, 765, 773-776 and 786-788. In specific embodiments, the polypeptides of the invention  
5 comprise amino acid sequences as set forth in any one of SEQ ID NO: 112-114, 172, 176, 178, 327, 329, 331, 336, 339, 376-380, 383, 477-483, 496, 504, 505, 519, 520, 522, 525, 527, 532, 534, 537-551, 553-568, 573-586, 588-590, 592, 627-629, 632, 633, 635, 637, 638, 656-671, 675, 683, 684, 710, 712, 714, 715, 717-719, 723-734, 736, 740-750, 752, 754, 755, 766-772, 777-785 and 789-791.

10 The polypeptides of the present invention are sometimes herein referred to as prostate-specific proteins or prostate-specific polypeptides, as an indication that their identification has been based at least in part upon their increased levels of expression in prostate tissue samples. Thus, a "prostate-specific polypeptide" or "prostate-specific protein," refers generally to a polypeptide sequence of the present  
15 invention, or a polynucleotide sequence encoding such a polypeptide, that is expressed in a substantial proportion of prostate tissue samples, for example preferably greater than about 20%, more preferably greater than about 30%, and most preferably greater than about 50% or more of prostate tissue samples tested, at a level that is at least two fold, and preferably at least five fold, greater than the level of expression in other  
20 normal tissues, as determined using a representative assay provided herein. A prostate-specific polypeptide sequence of the invention, based upon its increased level of expression in tumor cells, has particular utility both as a diagnostic marker as well as a therapeutic target, as further described below.

In certain preferred embodiments, the polypeptides of the invention are  
25 immunogenic, *i.e.*, they react detectably within an immunoassay (such as an ELISA or T-cell stimulation assay) with antisera and/or T-cells from a patient with prostate cancer. Screening for immunogenic activity can be performed using techniques well known to the skilled artisan. For example, such screens can be performed using methods such as those described in Harlow and Lane, *Antibodies: A Laboratory  
30 Manual*. Cold Spring Harbor Laboratory, 1988. In one illustrative example, a

polypeptide may be immobilized on a solid support and contacted with patient sera to allow binding of antibodies within the sera to the immobilized polypeptide. Unbound sera may then be removed and bound antibodies detected using, for example,  $^{125}\text{I}$ -labeled Protein A.

- 5                   As would be recognized by the skilled artisan, immunogenic portions of the polypeptides disclosed herein are also encompassed by the present invention. An "immunogenic portion," as used herein, is a fragment of an immunogenic polypeptide of the invention that itself is immunologically reactive (*i.e.*, specifically binds) with the B-cells and/or T-cell surface antigen receptors that recognize the polypeptide.
- 10   Immunogenic portions may generally be identified using well known techniques, such as those summarized in Paul, *Fundamental Immunology*, 3rd ed., 243-247 (Raven Press, 1993) and references cited therein. Such techniques include screening polypeptides for the ability to react with antigen-specific antibodies, antisera and/or T-cell lines or clones. As used herein, antisera and antibodies are "antigen-specific" if they
- 15   specifically bind to an antigen (*i.e.*, they react with the protein in an ELISA or other immunoassay, and do not react detectably with unrelated proteins). Such antisera and antibodies may be prepared as described herein, and using well-known techniques.

- In one preferred embodiment, an immunogenic portion of a polypeptide of the present invention is a portion that reacts with antisera and/or T-cells at a level that
- 20   is not substantially less than the reactivity of the full-length polypeptide (*e.g.*, in an ELISA and/or T-cell reactivity assay). Preferably, the level of immunogenic activity of the immunogenic portion is at least about 50%, preferably at least about 70% and most preferably greater than about 90% of the immunogenicity for the full-length polypeptide. In some instances, preferred immunogenic portions will be identified that
- 25   have a level of immunogenic activity greater than that of the corresponding full-length polypeptide, *e.g.*, having greater than about 100% or 150% or more immunogenic activity.

- In certain other embodiments, illustrative immunogenic portions may include peptides in which an N-terminal leader sequence and/or transmembrane domain
- 30   has been deleted. Other illustrative immunogenic portions will contain a small N-

and/or C-terminal deletion (*e.g.*, 1-30 amino acids, preferably 5-15 amino acids), relative to the mature protein.

In another embodiment, a polypeptide composition of the invention may also comprise one or more polypeptides that are immunologically reactive with T cells  
5 and/or antibodies generated against a polypeptide of the invention, particularly a polypeptide having an amino acid sequence disclosed herein, or to an immunogenic fragment or variant thereof.

In another embodiment of the invention, polypeptides are provided that comprise one or more polypeptides that are capable of eliciting T cells and/or antibodies  
10 that are immunologically reactive with one or more polypeptides described herein, or one or more polypeptides encoded by contiguous nucleic acid sequences contained in the polynucleotide sequences disclosed herein, or immunogenic fragments or variants thereof, or to one or more nucleic acid sequences which hybridize to one or more of these sequences under conditions of moderate to high stringency.

The present invention, in another aspect, provides polypeptide fragments  
15 comprising at least about 5, 10, 15, 20, 25, 50, or 100 contiguous amino acids, or more, including all intermediate lengths, of a polypeptide composition set forth herein, such as those set forth in SEQ ID NO: 112-114, 172, 176, 178, 327, 329, 331, 336, 339, 376-380, 383, 477-483, 496, 504, 505, 519, 520, 522, 525, 527, 532, 534, 537-551, 553-568,  
20 573-586, 588-590, 592, 627-629, 632, 633, 635, 637, 638, 656-671, 675, 683, 684, 710, 712, 714, 715, 717-719, 723-734, 736, 740-750, 752, 754, 755, 766-772, 777-785 and 789-791, or those encoded by a polynucleotide sequence set forth in a sequence of SEQ ID NO: 1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 and 384-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591,  
25 593-606, 618-626, 630, 631, 634, 636, 639-655, 674, 680, 681, 711, 713, 716, 720-722, 735, 737-739, 751, 753, 764, 765, 773-776 and 786-788.

In another aspect, the present invention provides variants of the polypeptide compositions described herein. Polypeptide variants generally encompassed by the present invention will typically exhibit at least about 70%, 75%,  
30 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% or more identity

(determined as described below), along its length, to a polypeptide sequence set forth herein.

In one preferred embodiment, the polypeptide fragments and variants provided by the present invention are immunologically reactive with an antibody and/or  
5 T-cell that reacts with a full-length polypeptide specifically set forth herein.

In another preferred embodiment, the polypeptide fragments and variants provided by the present invention exhibit a level of immunogenic activity of at least about 50%, preferably at least about 70%, and most preferably at least about 90% or more of that exhibited by a full-length polypeptide sequence specifically set forth  
10 herein.

A polypeptide "variant," as the term is used herein, is a polypeptide that typically differs from a polypeptide specifically disclosed herein in one or more substitutions, deletions, additions and/or insertions. Such variants may be naturally occurring or may be synthetically generated, for example, by modifying one or more of  
15 the above polypeptide sequences of the invention and evaluating their immunogenic activity as described herein using any of a number of techniques well known in the art.

For example, certain illustrative variants of the polypeptides of the invention include those in which one or more portions, such as an N-terminal leader sequence or transmembrane domain, have been removed. Other illustrative variants  
20 include variants in which a small portion (*e.g.*, 1-30 amino acids, preferably 5-15 amino acids) has been removed from the N- and/or C-terminal of the mature protein.

In many instances, a variant will contain conservative substitutions. A "conservative substitution" is one in which an amino acid is substituted for another amino acid that has similar properties, such that one skilled in the art of peptide  
25 chemistry would expect the secondary structure and hydropathic nature of the polypeptide to be substantially unchanged. As described above, modifications may be made in the structure of the polynucleotides and polypeptides of the present invention and still obtain a functional molecule that encodes a variant or derivative polypeptide with desirable characteristics, *e.g.*, with immunogenic characteristics. When it is  
30 desired to alter the amino acid sequence of a polypeptide to create an equivalent, or



even an improved, immunogenic variant or portion of a polypeptide of the invention, one skilled in the art will typically change one or more of the codons of the encoding DNA sequence according to Table 1.

For example, certain amino acids may be substituted for other amino acids in a protein structure without appreciable loss of interactive binding capacity with structures such as, for example, antigen-binding regions of antibodies or binding sites on substrate molecules. Since it is the interactive capacity and nature of a protein that defines that protein's biological functional activity, certain amino acid sequence substitutions can be made in a protein sequence, and, of course, its underlying DNA coding sequence, and nevertheless obtain a protein with like properties. It is thus contemplated that various changes may be made in the peptide sequences of the disclosed compositions, or corresponding DNA sequences which encode said peptides without appreciable loss of their biological utility or activity.

TABLE 1

Amino Acids			Codons					
Alanine	Ala	A	GCA	GCC	GCG	GCU		
Cysteine	Cys	C	UGC	UGU				
Aspartic acid	Asp	D	GAC	GAU				
Glutamic acid	Glu	E	GAA	GAG				
Phenylalanine	Phe	F	UUC	UUU				
Glycine	Gly	G	GGA	GGC	GGG	GGU		
Histidine	His	H	CAC	CAU				
Isoleucine	Ile	I	AUA	AUC	AUU			
Lysine	Lys	K	AAA	AAG				
Leucine	Leu	L	UUA	UUG	CUA	CUC	CUG	CUU
Methionine	Met	M	AUG					
Asparagine	Asn	N	AAC	AAU				
Proline	Pro	P	CCA	CCC	CCG	CCU		
Glutamine	Gln	Q	CAA	CAG				
Arginine	Arg	R	AGA	AGG	CGA	CGC	CGG	CGU
Serine	Ser	S	AGC	AGU	UCA	UCC	UCG	UCU
Threonine	Thr	T	ACA	ACC	ACG	ACU		
Valine	Val	V	GUA	GUC	GUG	GUU		
Tryptophan	Trp	W	UGG					
Tyrosine	Tyr	Y	UAC	UAU				

In making such changes, the hydropathic index of amino acids may be considered. The importance of the hydropathic amino acid index in conferring interactive biologic function on a protein is generally understood in the art (Kyte and Doolittle, 1982, incorporated herein by reference). It is accepted that the relative hydropathic character of the amino acid contributes to the secondary structure of the resultant protein, which in turn defines the interaction of the protein with other molecules, for example, enzymes, substrates, receptors, DNA, antibodies, antigens, and the like. Each amino acid has been assigned a hydropathic index on the basis of its

hydrophobicity and charge characteristics (Kyte and Doolittle, 1982). These values are: isoleucine (+4.5); valine (+4.2); leucine (+3.8); phenylalanine (+2.8); cysteine/cystine (+2.5); methionine (+1.9); alanine (+1.8); glycine (-0.4); threonine (-0.7); serine (-0.8); tryptophan (-0.9); tyrosine (-1.3); proline (-1.6); histidine (-3.2); glutamate (-3.5);  
5 glutamine (-3.5); aspartate (-3.5); asparagine (-3.5); lysine (-3.9); and arginine (-4.5).

It is known in the art that certain amino acids may be substituted by other amino acids having a similar hydropathic index or score and still result in a protein with similar biological activity, *i.e.* still obtain a biological functionally equivalent protein. In making such changes, the substitution of amino acids whose hydropathic indices are  
10 within  $\pm 2$  is preferred, those within  $\pm 1$  are particularly preferred, and those within  $\pm 0.5$  are even more particularly preferred. It is also understood in the art that the substitution of like amino acids can be made effectively on the basis of hydrophilicity. U.S. Patent 4,554,101 (specifically incorporated herein by reference in its entirety), states that the greatest local average hydrophilicity of a protein, as governed by the hydrophilicity of  
15 its adjacent amino acids, correlates with a biological property of the protein.

As detailed in U. S. Patent 4,554,101, the following hydrophilicity values have been assigned to amino acid residues: arginine (+3.0); lysine (+3.0); aspartate (+3.0  $\pm$  1); glutamate (+3.0  $\pm$  1); serine (+0.3); asparagine (+0.2); glutamine (+0.2); glycine (0); threonine (-0.4); proline (-0.5  $\pm$  1); alanine (-0.5); histidine (-0.5); cysteine  
20 (-1.0); methionine (-1.3); valine (-1.5); leucine (-1.8); isoleucine (-1.8); tyrosine (-2.3); phenylalanine (-2.5); tryptophan (-3.4). It is understood that an amino acid can be substituted for another having a similar hydrophilicity value and still obtain a biologically equivalent, and in particular, an immunologically equivalent protein. In such changes, the substitution of amino acids whose hydrophilicity values are within  $\pm 2$   
25 is preferred, those within  $\pm 1$  are particularly preferred, and those within  $\pm 0.5$  are even more particularly preferred.

As outlined above, amino acid substitutions are generally therefore based on the relative similarity of the amino acid side-chain substituents, for example, their hydrophobicity, hydrophilicity, charge, size, and the like. Exemplary substitutions that  
30 take various of the foregoing characteristics into consideration are well known to those

of skill in the art and include: arginine and lysine; glutamate and aspartate; serine and threonine; glutamine and asparagine; and valine, leucine and isoleucine.

In addition, any polynucleotide may be further modified to increase stability *in vivo*. Possible modifications include, but are not limited to, the addition of  
5 flanking sequences at the 5' and/or 3' ends; the use of phosphorothioate or 2' O-methyl rather than phosphodiesterase linkages in the backbone; and/or the inclusion of nontraditional bases such as inosine, queosine and wybutosine, as well as acetyl-methyl-, thio- and other modified forms of adenine, cytidine, guanine, thymine and uridine.

10 Amino acid substitutions may further be made on the basis of similarity in polarity, charge, solubility, hydrophobicity, hydrophilicity and/or the amphipathic nature of the residues. For example, negatively charged amino acids include aspartic acid and glutamic acid; positively charged amino acids include lysine and arginine; and amino acids with uncharged polar head groups having similar hydrophilicity values  
15 include leucine, isoleucine and valine; glycine and alanine; asparagine and glutamine; and serine, threonine, phenylalanine and tyrosine. Other groups of amino acids that may represent conservative changes include: (1) ala, pro, gly, glu, asp, gln, asn, ser, thr; (2) cys, ser, tyr, thr; (3) val, ile, leu, met, ala, phe; (4) lys, arg, his; and (5) phe, tyr, trp, his. A variant may also, or alternatively, contain nonconservative changes. In a  
20 preferred embodiment, variant polypeptides differ from a native sequence by substitution, deletion or addition of five amino acids or fewer. Variants may also (or alternatively) be modified by, for example, the deletion or addition of amino acids that have minimal influence on the immunogenicity, secondary structure and hydrophobic nature of the polypeptide.

25 As noted above, polypeptides may comprise a signal (or leader) sequence at the N-terminal end of the protein, which co-translationally or post-translationally directs transfer of the protein. The polypeptide may also be conjugated to a linker or other sequence for ease of synthesis, purification or identification of the polypeptide (e.g., poly-His), or to enhance binding of the polypeptide to a solid support. For  
30 example, a polypeptide may be conjugated to an immunoglobulin Fc region.

When comparing polypeptide sequences, two sequences are said to be "identical" if the sequence of amino acids in the two sequences is the same when aligned for maximum correspondence, as described below. Comparisons between two sequences are typically performed by comparing the sequences over a comparison window to identify and compare local regions of sequence similarity. A "comparison window" as used herein, refers to a segment of at least about 20 contiguous positions, usually 30 to about 75, 40 to about 50, in which a sequence may be compared to a reference sequence of the same number of contiguous positions after the two sequences are optimally aligned.

- Optimal alignment of sequences for comparison may be conducted using the Megalign program in the Lasergene suite of bioinformatics software (DNASTAR, Inc., Madison, WI), using default parameters. This program embodies several alignment schemes described in the following references: Dayhoff, M.O. (1978) A model of evolutionary change in proteins – Matrices for detecting distant relationships. In Dayhoff, M.O. (ed.) *Atlas of Protein Sequence and Structure*, National Biomedical Research Foundation, Washington DC Vol. 5, Suppl. 3, pp. 345-358; Hein J. (1990) Unified Approach to Alignment and Phylogenies pp. 626-645 *Methods in Enzymology* vol. 183, Academic Press, Inc., San Diego, CA; Higgins, D.G. and Sharp, P.M. (1989) *CABIOS* 5:151-153; Myers, E.W. and Muller W. (1988) *CABIOS* 4:11-17; Robinson, E.D. (1971) *Comb. Theor* 11:105; Santou, N. Nes, M. (1987) *Mol. Biol. Evol.* 4:406-425; Sneath, P.H.A. and Sokal, R.R. (1973) *Numerical Taxonomy – the Principles and Practice of Numerical Taxonomy*, Freeman Press, San Francisco, CA; Wilbur, W.J. and Lipman, D.J. (1983) *Proc. Natl. Acad., Sci. USA* 80:726-730.

Alternatively, optimal alignment of sequences for comparison may be conducted by the local identity algorithm of Smith and Waterman (1981) *Add. APL. Math* 2:482, by the identity alignment algorithm of Needleman and Wunsch (1970) *J. Mol. Biol.* 48:443, by the search for similarity methods of Pearson and Lipman (1988) *Proc. Natl. Acad. Sci. USA* 85: 2444, by computerized implementations of these algorithms (GAP, BESTFIT, BLAST, FASTA, and TFASTA in the Wisconsin Genetics

Software Package, Genetics Computer Group (GCG), 575 Science Dr., Madison, WI), or by inspection.

One preferred example of algorithms that are suitable for determining percent sequence identity and sequence similarity are the BLAST and BLAST 2.0 algorithms, which are described in Altschul et al. (1977) *Nucl. Acids Res.* 25:3389-3402 and Altschul et al. (1990) *J. Mol. Biol.* 215:403-410, respectively. BLAST and BLAST 2.0 can be used, for example with the parameters described herein, to determine percent sequence identity for the polynucleotides and polypeptides of the invention. Software for performing BLAST analyses is publicly available through the National Center for Biotechnology Information. For amino acid sequences, a scoring matrix can be used to calculate the cumulative score. Extension of the word hits in each direction are halted when: the cumulative alignment score falls off by the quantity X from its maximum achieved value; the cumulative score goes to zero or below, due to the accumulation of one or more negative-scoring residue alignments; or the end of either sequence is reached. The BLAST algorithm parameters W, T and X determine the sensitivity and speed of the alignment.

In one preferred approach, the "percentage of sequence identity" is determined by comparing two optimally aligned sequences over a window of comparison of at least 20 positions, wherein the portion of the polypeptide sequence in the comparison window may comprise additions or deletions (*i.e.*, gaps) of 20 percent or less, usually 5 to 15 percent, or 10 to 12 percent, as compared to the reference sequences (which does not comprise additions or deletions) for optimal alignment of the two sequences. The percentage is calculated by determining the number of positions at which the identical amino acid residue occurs in both sequences to yield the number of matched positions, dividing the number of matched positions by the total number of positions in the reference sequence (*i.e.*, the window size) and multiplying the results by 100 to yield the percentage of sequence identity.

Within other illustrative embodiments, a polypeptide may be a fusion polypeptide that comprises multiple polypeptides as described herein, or that comprises at least one polypeptide as described herein and an unrelated sequence, such as a known

tumor protein. A fusion partner may, for example, assist in providing T helper epitopes (an immunological fusion partner), preferably T helper epitopes recognized by humans, or may assist in expressing the protein (an expression enhancer) at higher yields than the native recombinant protein. Certain preferred fusion partners are both immunological and expression enhancing fusion partners. Other fusion partners may be selected so as to increase the solubility of the polypeptide or to enable the polypeptide to be targeted to desired intracellular compartments. Still further fusion partners include affinity tags, which facilitate purification of the polypeptide.

Fusion polypeptides may generally be prepared using standard techniques, including chemical conjugation. Preferably, a fusion polypeptide is expressed as a recombinant polypeptide, allowing the production of increased levels, relative to a non-fused polypeptide, in an expression system. Briefly, DNA sequences encoding the polypeptide components may be assembled separately, and ligated into an appropriate expression vector. The 3' end of the DNA sequence encoding one polypeptide component is ligated, with or without a peptide linker, to the 5' end of a DNA sequence encoding the second polypeptide component so that the reading frames of the sequences are in phase. This permits translation into a single fusion polypeptide that retains the biological activity of both component polypeptides.

A peptide linker sequence may be employed to separate the first and second polypeptide components by a distance sufficient to ensure that each polypeptide folds into its secondary and tertiary structures. Such a peptide linker sequence is incorporated into the fusion polypeptide using standard techniques well known in the art. Suitable peptide linker sequences may be chosen based on the following factors: (1) their ability to adopt a flexible extended conformation; (2) their inability to adopt a secondary structure that could interact with functional epitopes on the first and second polypeptides; and (3) the lack of hydrophobic or charged residues that might react with the polypeptide functional epitopes. Preferred peptide linker sequences contain Gly, Asn and Ser residues. Other near neutral amino acids, such as Thr and Ala may also be used in the linker sequence. Amino acid sequences which may be usefully employed as linkers include those disclosed in Maratea et al., *Gene* 40:39-46, 1985; Murphy et al.,

*Proc. Natl. Acad. Sci. USA* 83:8258-8262, 1986; U.S. Patent No. 4,935,233 and U.S. Patent No. 4,751,180. The linker sequence may generally be from 1 to about 50 amino acids in length. Linker sequences are not required when the first and second polypeptides have non-essential N-terminal amino acid regions that can be used to  
5 separate the functional domains and prevent steric interference.

The ligated DNA sequences are operably linked to suitable transcriptional or translational regulatory elements. The regulatory elements responsible for expression of DNA are located only 5' to the DNA sequence encoding the first polypeptides. Similarly, stop codons required to end translation and  
10 transcription termination signals are only present 3' to the DNA sequence encoding the second polypeptide.

The fusion polypeptide can comprise a polypeptide as described herein together with an unrelated immunogenic protein, such as an immunogenic protein capable of eliciting a recall response. Examples of such proteins include tetanus,  
15 tuberculosis and hepatitis proteins (*see*, for example, Stoute et al. *New Engl. J. Med.*, 336:86-91, 1997).

In one preferred embodiment, the immunological fusion partner is derived from a *Mycobacterium* sp., such as a *Mycobacterium tuberculosis*-derived Ra12 fragment. Ra12 compositions and methods for their use in enhancing the expression  
20 and/or immunogenicity of heterologous polynucleotide/polypeptide sequences is described in U.S. Patent Application 60/158,585, the disclosure of which is incorporated herein by reference in its entirety. Briefly, Ra12 refers to a polynucleotide region that is a subsequence of a *Mycobacterium tuberculosis* MTB32A nucleic acid. MTB32A is a serine protease of 32 KD molecular weight encoded by a gene in virulent  
25 and avirulent strains of *M. tuberculosis*. The nucleotide sequence and amino acid sequence of MTB32A have been described (for example, U.S. Patent Application 60/158,585; *see also*, Skeiky et al., *Infection and Immun.* (1999) 67:3998-4007, incorporated herein by reference). C-terminal fragments of the MTB32A coding sequence express at high levels and remain as a soluble polypeptides throughout the  
30 purification process. Moreover, Ra12 may enhance the immunogenicity of heterologous



immunogenic polypeptides with which it is fused. One preferred Ra12 fusion polypeptide comprises a 14 KD C-terminal fragment corresponding to amino acid residues 192 to 323 of MTB32A. Other preferred Ra12 polynucleotides generally comprise at least about 15 consecutive nucleotides, at least about 30 nucleotides, at least  
5 about 60 nucleotides, at least about 100 nucleotides, at least about 200 nucleotides, or at least about 300 nucleotides that encode a portion of a Ra12 polypeptide. Ra12 polynucleotides may comprise a native sequence (*i.e.*, an endogenous sequence that encodes a Ra12 polypeptide or a portion thereof) or may comprise a variant of such a sequence. Ra12 polynucleotide variants may contain one or more substitutions,  
10 additions, deletions and/or insertions such that the biological activity of the encoded fusion polypeptide is not substantially diminished, relative to a fusion polypeptide comprising a native Ra12 polypeptide. Variants preferably exhibit at least about 70% identity, more preferably at least about 80% identity and most preferably at least about 90% identity to a polynucleotide sequence that encodes a native Ra12 polypeptide or a  
15 portion thereof.

Within other preferred embodiments, an immunological fusion partner is derived from protein D, a surface protein of the gram-negative bacterium *Haemophilus influenza B* (WO 91/18926). Preferably, a protein D derivative comprises approximately the first third of the protein (*e.g.*, the first N-terminal 100-110 amino  
20 acids), and a protein D derivative may be lipidated. Within certain preferred embodiments, the first 109 residues of a Lipoprotein D fusion partner is included on the N-terminus to provide the polypeptide with additional exogenous T-cell epitopes and to increase the expression level in *E. coli* (thus functioning as an expression enhancer). The lipid tail ensures optimal presentation of the antigen to antigen presenting cells.  
25 Other fusion partners include the non-structural protein from influenzae virus, NS1 (hemagglutinin). Typically, the N-terminal 81 amino acids are used, although different fragments that include T-helper epitopes may be used.

In another embodiment, the immunological fusion partner is the protein known as LYTA, or a portion thereof (preferably a C-terminal portion). LYTA is  
30 derived from *Streptococcus pneumoniae*, which synthesizes an N-acetyl-L-alanine

amidase known as amidase LYTA (encoded by the *LytA* gene; *Gene* 43:265-292, 1986). LYTA is an autolysin that specifically degrades certain bonds in the peptidoglycan backbone. The C-terminal domain of the LYTA protein is responsible for the affinity to the choline or to some choline analogues such as DEAE. This property has been  
5 exploited for the development of *E. coli* C-LYTA expressing plasmids useful for expression of fusion proteins. Purification of hybrid proteins containing the C-LYTA fragment at the amino terminus has been described (see *Biotechnology* 10:795-798, 1992). Within a preferred embodiment, a repeat portion of LYTA may be incorporated into a fusion polypeptide. A repeat portion is found in the C-terminal region starting at  
10 residue 178. A particularly preferred repeat portion incorporates residues 188-305.

Yet another illustrative embodiment involves fusion polypeptides, and the polynucleotides encoding them, wherein the fusion partner comprises a targeting signal capable of directing a polypeptide to the endosomal/lysosomal compartment, as described in U.S. Patent No. 5,633,234. An immunogenic polypeptide of the invention,  
15 when fused with this targeting signal, will associate more efficiently with MHC class II molecules and thereby provide enhanced in vivo stimulation of CD4<sup>+</sup> T-cells specific for the polypeptide.

Polypeptides of the invention are prepared using any of a variety of well known synthetic and/or recombinant techniques, the latter of which are further  
20 described below. Polypeptides, portions and other variants generally less than about 150 amino acids can be generated by synthetic means, using techniques well known to those of ordinary skill in the art. In one illustrative example, such polypeptides are synthesized using any of the commercially available solid-phase techniques, such as the Merrifield solid-phase synthesis method, where amino acids are sequentially added to a  
25 growing amino acid chain. See Merrifield, *J. Am. Chem. Soc.* 85:2149-2146, 1963. Equipment for automated synthesis of polypeptides is commercially available from suppliers such as Perkin Elmer/Applied BioSystems Division (Foster City, CA), and may be operated according to the manufacturer's instructions.

In general, polypeptide compositions (including fusion polypeptides) of  
30 the invention are isolated. An "isolated" polypeptide is one that is removed from its

original environment. For example, a naturally-occurring protein or polypeptide is isolated if it is separated from some or all of the coexisting materials in the natural system. Preferably, such polypeptides are also purified, *e.g.*, are at least about 90% pure, more preferably at least about 95% pure and most preferably at least about 99%  
5 pure.

#### Polynucleotide Compositions

The present invention, in other aspects, provides polynucleotide compositions. The terms "DNA" and "polynucleotide" are used essentially interchangeably herein to refer to a DNA molecule that has been isolated free of total  
10 genomic DNA of a particular species. "Isolated," as used herein, means that a polynucleotide is substantially away from other coding sequences, and that the DNA molecule does not contain large portions of unrelated coding DNA, such as large chromosomal fragments or other functional genes or polypeptide coding regions. Of course, this refers to the DNA molecule as originally isolated, and does not exclude  
15 genes or coding regions later added to the segment by the hand of man.

As will be understood by those skilled in the art, the polynucleotide compositions of this invention can include genomic sequences, extra-genomic and plasmid-encoded sequences and smaller engineered gene segments that express, or may be adapted to express, proteins, polypeptides, peptides and the like. Such segments may  
20 be naturally isolated, or modified synthetically by the hand of man.

As will be also recognized by the skilled artisan, polynucleotides of the invention may be single-stranded (coding or antisense) or double-stranded, and may be DNA (genomic, cDNA or synthetic) or RNA molecules. RNA molecules may include  
25 tRNA molecules, which contain introns and correspond to a DNA molecule in a one-to-one manner, and mRNA molecules, which do not contain introns. Additional coding or non-coding sequences may, but need not, be present within a polynucleotide of the present invention, and a polynucleotide may, but need not, be linked to other molecules and/or support materials.

Polynucleotides may comprise a native sequence (*i.e.*, an endogenous sequence that encodes a polypeptide/protein of the invention or a portion thereof) or may comprise a sequence that encodes a variant or derivative, preferably an immunogenic variant or derivative, of such a sequence.

5           Therefore, according to another aspect of the present invention, polynucleotide compositions are provided that comprise some or all of a polynucleotide sequence set forth in any one of SEQ ID NOs: 1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 and 384-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-626, 630, 631, 634, 636, 639-655, 10 674, 680, 681, 711, 713, 716, 720-722, 735, 737-739, 751, 753, 764, 765, 773-776 and 786-788, complements of a polynucleotide sequence set forth in any one of SEQ ID NOs: 1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 and 384-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-626, 630, 631, 634, 636, 639-655, 674, 680, 681, 711, 713, 716, 720-722, 15 735, 737-739, 751, 753, 764, 765, 773-776 and 786-788, and degenerate variants of a polynucleotide sequence set forth in any one of SEQ ID NOs: 1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 and 384-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-626, 630, 631, 634, 636, 639-655, 674, 680, 681, 711, 713, 716, 720-722, 735, 737-739, 751, 753, 764, 765, 20 773-776 and 786-788. In certain preferred embodiments, the polynucleotide sequences set forth herein encode immunogenic polypeptides, as described above.

          In other related embodiments, the present invention provides polynucleotide variants having substantial identity to the sequences disclosed herein in SEQ ID NOs: 1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332- 25 335, 340-375, 381, 382 and 384-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-626, 630, 631, 634, 636, 639-655, 674, 680, 681, 711, 713, 716, 720-722, 735, 737-739, 751, 753, 764, 765, 773-776 and 786-788, for example those comprising at least 70% sequence identity, preferably at least 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% or higher, sequence identity compared to a 30 polynucleotide sequence of this invention using the methods described herein, (*e.g.*,

BLAST analysis using standard parameters, as described below). One skilled in this art will recognize that these values can be appropriately adjusted to determine corresponding identity of proteins encoded by two nucleotide sequences by taking into account codon degeneracy, amino acid similarity, reading frame positioning and the like.

Typically, polynucleotide variants will contain one or more substitutions, additions, deletions and/or insertions, preferably such that the immunogenicity of the polypeptide encoded by the variant polynucleotide is not substantially diminished relative to a polypeptide encoded by a polynucleotide sequence specifically set forth herein). The term "variants" should also be understood to encompass homologous genes of xenogenic origin.

In additional embodiments, the present invention provides polynucleotide fragments comprising various lengths of contiguous stretches of sequence identical to, or complementary to, one or more of the sequences disclosed herein. For example, polynucleotides are provided by this invention that comprise at least about 10, 15, 20, 30, 40, 50, 75, 100, 150, 200, 300, 400, 500 or 1000 or more contiguous nucleotides of one or more of the sequences disclosed herein as well as all intermediate lengths there between. It will be readily understood that "intermediate lengths", in this context, means any length between the quoted values, such as 16, 17, 18, 19, *etc.*; 21, 22, 23, *etc.*; 30, 31, 32, *etc.*; 50, 51, 52, 53, *etc.*; 100, 101, 102, 103, *etc.*; 150, 151, 152, 153, *etc.*; including all integers through 200-500; 500-1,000, and the like.

In another embodiment of the invention, polynucleotide compositions are provided that are capable of hybridizing under moderate to high stringency conditions to a polynucleotide sequence provided herein, or a fragment thereof, or a complementary sequence thereof. Hybridization techniques are well known in the art of molecular biology. For purposes of illustration, suitable moderately stringent conditions for testing the hybridization of a polynucleotide of this invention with other polynucleotides include prewashing in a solution of 5 X SSC, 0.5% SDS, 1.0 mM EDTA (pH 8.0); hybridizing at 50°C-60°C, 5 X SSC, overnight; followed by washing twice at 65°C for

20 minutes with each of 2X, 0.5X and 0.2X SSC containing 0.1% SDS. One skilled in the art will understand that the stringency of hybridization can be readily manipulated, such as by altering the salt content of the hybridization solution and/or the temperature at which the hybridization is performed. For example, in another embodiment, suitable highly stringent hybridization conditions include those described above, with the exception that the temperature of hybridization is increased, *e.g.*, to 60-65°C or 65-70°C.

In certain preferred embodiments, the polynucleotides described above, *e.g.*, polynucleotide variants, fragments and hybridizing sequences, encode polypeptides that are immunologically cross-reactive with a polypeptide sequence specifically set forth herein. In other preferred embodiments, such polynucleotides encode polypeptides that have a level of immunogenic activity of at least about 50%, preferably at least about 70%, and more preferably at least about 90% of that for a polypeptide sequence specifically set forth herein.

The polynucleotides of the present invention, or fragments thereof, regardless of the length of the coding sequence itself, may be combined with other DNA sequences, such as promoters, polyadenylation signals, additional restriction enzyme sites, multiple cloning sites, other coding segments, and the like, such that their overall length may vary considerably. It is therefore contemplated that a nucleic acid fragment of almost any length may be employed, with the total length preferably being limited by the ease of preparation and use in the intended recombinant DNA protocol. For example, illustrative polynucleotide segments with total lengths of about 10,000, about 5000, about 3000, about 2,000, about 1,000, about 500, about 200, about 100, about 50 base pairs in length, and the like, (including all intermediate lengths) are contemplated to be useful in many implementations of this invention.

When comparing polynucleotide sequences, two sequences are said to be "identical" if the sequence of nucleotides in the two sequences is the same when aligned for maximum correspondence, as described below. Comparisons between two sequences are typically performed by comparing the sequences over a comparison window to identify and compare local regions of sequence similarity. A "comparison

window" as used herein, refers to a segment of at least about 20 contiguous positions, usually 30 to about 75, preferably 40 to about 50, in which a sequence may be compared to a reference sequence of the same number of contiguous positions after the two sequences are optimally aligned.

- 5           Optimal alignment of sequences for comparison may be conducted using the Megalign program in the Lasergene suite of bioinformatics software (DNASTAR, Inc., Madison, WI), using default parameters. This program embodies several alignment schemes described in the following references: Dayhoff, M.O. (1978) A model of evolutionary change in proteins – Matrices for detecting distant relationships.
- 10 In Dayhoff, M.O. (ed.) *Atlas of Protein Sequence and Structure*, National Biomedical Research Foundation, Washington DC Vol. 5, Suppl. 3, pp. 345-358; Hein J. (1990) *Unified Approach to Alignment and Phylogenies* pp. 626-645 *Methods in Enzymology* vol. 183, Academic Press, Inc., San Diego, CA; Higgins, D.G. and Sharp, P.M. (1989) *CABIOS* 5:151-153; Myers, E.W. and Muller W. (1988) *CABIOS* 4:11-17; Robinson,
- 15 E.D. (1971) *Comb. Theor* 11:105; Santou, N. Nes, M. (1987) *Mol. Biol. Evol.* 4:406-425; Sneath, P.H.A. and Sokal, R.R. (1973) *Numerical Taxonomy – the Principles and Practice of Numerical Taxonomy*, Freeman Press, San Francisco, CA; Wilbur, W.J. and Lipman, D.J. (1983) *Proc. Natl. Acad., Sci. USA* 80:726-730.

- Alternatively, optimal alignment of sequences for comparison may be
- 20 conducted by the local identity algorithm of Smith and Waterman (1981) *Add. APL. Math* 2:482, by the identity alignment algorithm of Needleman and Wunsch (1970) *J. Mol. Biol.* 48:443, by the search for similarity methods of Pearson and Lipman (1988) *Proc. Natl. Acad. Sci. USA* 85: 2444, by computerized implementations of these algorithms (GAP, BESTFIT, BLAST, FASTA, and TFASTA in the Wisconsin Genetics
- 25 Software Package, Genetics Computer Group (GCG), 575 Science Dr., Madison, WI), or by inspection.

- One preferred example of algorithms that are suitable for determining percent sequence identity and sequence similarity are the BLAST and BLAST 2.0 algorithms, which are described in Altschul et al. (1977) *Nucl. Acids Res.* 25:3389-3402
- 30 and Altschul et al. (1990) *J. Mol. Biol.* 215:403-410, respectively. BLAST and BLAST

2.0 can be used, for example with the parameters described herein, to determine percent sequence identity for the polynucleotides of the invention. Software for performing **BLAST** analyses is publicly available through the National Center for Biotechnology Information. In one illustrative example, cumulative scores can be calculated using, for  
5 nucleotide sequences, the parameters M (reward score for a pair of matching residues; always >0) and N (penalty score for mismatching residues; always <0). Extension of the word hits in each direction are halted when: the cumulative alignment score falls off by the quantity X from its maximum achieved value; the cumulative score goes to zero or below, due to the accumulation of one or more negative-scoring residue alignments;  
10 or the end of either sequence is reached. The BLAST algorithm parameters W, T and X determine the sensitivity and speed of the alignment. The BLASTN program (for nucleotide sequences) uses as defaults a wordlength (W) of 11, and expectation (E) of 10, and the BLOSUM62 scoring matrix (see Henikoff and Henikoff (1989) *Proc. Natl. Acad. Sci. USA* 89:10915) alignments, (B) of 50, expectation (E) of 10, M=5, N=-4 and  
15 a comparison of both strands.

Preferably, the "percentage of sequence identity" is determined by comparing two optimally aligned sequences over a window of comparison of at least 20 positions, wherein the portion of the polynucleotide sequence in the comparison window may comprise additions or deletions (*i.e.*, gaps) of 20 percent or less, usually 5  
20 to 15 percent, or 10 to 12 percent, as compared to the reference sequences (which does not comprise additions or deletions) for optimal alignment of the two sequences. The percentage is calculated by determining the number of positions at which the identical nucleic acid bases occurs in both sequences to yield the number of matched positions, dividing the number of matched positions by the total number of positions in the  
25 reference sequence (*i.e.*, the window size) and multiplying the results by 100 to yield the percentage of sequence identity.

It will be appreciated by those of ordinary skill in the art that, as a result of the degeneracy of the genetic code, there are many nucleotide sequences that encode a polypeptide as described herein. Some of these polynucleotides bear minimal  
30 homology to the nucleotide sequence of any native gene. Nonetheless, polynucleotides



that vary due to differences in codon usage are specifically contemplated by the present invention. Further, alleles of the genes comprising the polynucleotide sequences provided herein are within the scope of the present invention. Alleles are endogenous genes that are altered as a result of one or more mutations, such as deletions, additions  
5 and/or substitutions of nucleotides. The resulting mRNA and protein may, but need not, have an altered structure or function. Alleles may be identified using standard techniques (such as hybridization, amplification and/or database sequence comparison).

Therefore, in another embodiment of the invention, a mutagenesis approach, such as site-specific mutagenesis, is employed for the preparation of  
10 immunogenic variants and/or derivatives of the polypeptides described herein. By this approach, specific modifications in a polypeptide sequence can be made through mutagenesis of the underlying polynucleotides that encode them. These techniques provides a straightforward approach to prepare and test sequence variants, for example, incorporating one or more of the foregoing considerations, by introducing one or more  
15 nucleotide sequence changes into the polynucleotide.

Site-specific mutagenesis allows the production of mutants through the use of specific oligonucleotide sequences which encode the DNA sequence of the desired mutation, as well as a sufficient number of adjacent nucleotides, to provide a primer sequence of sufficient size and sequence complexity to form a stable duplex on  
20 both sides of the deletion junction being traversed. Mutations may be employed in a selected polynucleotide sequence to improve, alter, decrease, modify, or otherwise change the properties of the polynucleotide itself, and/or alter the properties, activity, composition, stability, or primary sequence of the encoded polypeptide.

In certain embodiments of the present invention, the inventors  
25 contemplate the mutagenesis of the disclosed polynucleotide sequences to alter one or more properties of the encoded polypeptide, such as the immunogenicity of a polypeptide vaccine. The techniques of site-specific mutagenesis are well-known in the art, and are widely used to create variants of both polypeptides and polynucleotides. For example, site-specific mutagenesis is often used to alter a specific portion of a DNA  
30 molecule. In such embodiments, a primer comprising typically about 14 to about 25

nucleotides or so in length is employed, with about 5 to about 10 residues on both sides of the junction of the sequence being altered.

As will be appreciated by those of skill in the art, site-specific mutagenesis techniques have often employed a phage vector that exists in both a single  
5 stranded and double stranded form. Typical vectors useful in site-directed mutagenesis include vectors such as the M13 phage. These phage are readily commercially-available and their use is generally well-known to those skilled in the art. Double-stranded plasmids are also routinely employed in site directed mutagenesis that eliminates the step of transferring the gene of interest from a plasmid to a phage.

10 In general, site-directed mutagenesis in accordance herewith is performed by first obtaining a single-stranded vector or melting apart of two strands of a double-stranded vector that includes within its sequence a DNA sequence that encodes the desired peptide. An oligonucleotide primer bearing the desired mutated sequence is prepared, generally synthetically. This primer is then annealed with the single-stranded  
15 vector, and subjected to DNA polymerizing enzymes such as *E. coli* polymerase I Klenow fragment, in order to complete the synthesis of the mutation-bearing strand. Thus, a heteroduplex is formed wherein one strand encodes the original non-mutated sequence and the second strand bears the desired mutation. This heteroduplex vector is then used to transform appropriate cells, such as *E. coli* cells, and clones are selected  
20 which include recombinant vectors bearing the mutated sequence arrangement.

The preparation of sequence variants of the selected peptide-encoding DNA segments using site-directed mutagenesis provides a means of producing potentially useful species and is not meant to be limiting as there are other ways in which sequence variants of peptides and the DNA sequences encoding them may be  
25 obtained. For example, recombinant vectors encoding the desired peptide sequence may be treated with mutagenic agents, such as hydroxylamine, to obtain sequence variants. Specific details regarding these methods and protocols are found in the teachings of Maloy *et al.*, 1994; Segal, 1976; Prokop and Bajpai, 1991; Kuby, 1994; and Maniatis *et al.*, 1982, each incorporated herein by reference, for that purpose.

As used herein, the term "oligonucleotide directed mutagenesis procedure" refers to template-dependent processes and vector-mediated propagation which result in an increase in the concentration of a specific nucleic acid molecule relative to its initial concentration, or in an increase in the concentration of a detectable  
5 signal, such as amplification. As used herein, the term "oligonucleotide directed mutagenesis procedure" is intended to refer to a process that involves the template-dependent extension of a primer molecule. The term template dependent process refers to nucleic acid synthesis of an RNA or a DNA molecule wherein the sequence of the newly synthesized strand of nucleic acid is dictated by the well-known  
10 rules of complementary base pairing (see, for example, Watson, 1987). Typically, vector mediated methodologies involve the introduction of the nucleic acid fragment into a DNA or RNA vector, the clonal amplification of the vector, and the recovery of the amplified nucleic acid fragment. Examples of such methodologies are provided by U. S. Patent No. 4,237,224, specifically incorporated herein by reference in its entirety.

15 In another approach for the production of polypeptide variants of the present invention, recursive sequence recombination, as described in U.S. Patent No. 5,837,458, may be employed. In this approach, iterative cycles of recombination and screening or selection are performed to "evolve" individual polynucleotide variants of the invention having, for example, enhanced immunogenic activity.

20 In other embodiments of the present invention, the polynucleotide sequences provided herein can be advantageously used as probes or primers for nucleic acid hybridization. As such, it is contemplated that nucleic acid segments that comprise a sequence region of at least about 15 contiguous nucleotides that has the same sequence as, or is complementary to, a 15 nucleotide long contiguous sequence  
25 disclosed herein will find particular utility. Longer contiguous identical or complementary sequences, *e.g.*, those of about 20, 30, 40, 50, 100, 200, 500, 1000 (including all intermediate lengths) and even up to full length sequences will also be of use in certain embodiments.

The ability of such nucleic acid probes to specifically hybridize to a  
30 sequence of interest will enable them to be of use in detecting the presence of

complementary sequences in a given sample. However, other uses are also envisioned, such as the use of the sequence information for the preparation of mutant species primers, or primers for use in preparing other genetic constructions.

Polynucleotide molecules having sequence regions consisting of  
5 contiguous nucleotide stretches of 10-14, 15-20, 30, 50, or even of 100-200 nucleotides or so (including intermediate lengths as well), identical or complementary to a polynucleotide sequence disclosed herein, are particularly contemplated as hybridization probes for use in, *e.g.*, Southern and Northern blotting. This would allow a gene product, or fragment thereof, to be analyzed, both in diverse cell types and also in  
10 various bacterial cells. The total size of fragment, as well as the size of the complementary stretch(es), will ultimately depend on the intended use or application of the particular nucleic acid segment. Smaller fragments will generally find use in hybridization embodiments, wherein the length of the contiguous complementary region may be varied, such as between about 15 and about 100 nucleotides, but larger  
15 contiguous complementarity stretches may be used, according to the length complementary sequences one wishes to detect.

The use of a hybridization probe of about 15-25 nucleotides in length allows the formation of a duplex molecule that is both stable and selective. Molecules having contiguous complementary sequences over stretches greater than 15 bases in  
20 length are generally preferred, though, in order to increase stability and selectivity of the hybrid, and thereby improve the quality and degree of specific hybrid molecules obtained. One will generally prefer to design nucleic acid molecules having gene-complementary stretches of 15 to 25 contiguous nucleotides, or even longer where desired.

25 Hybridization probes may be selected from any portion of any of the sequences disclosed herein. All that is required is to review the sequences set forth herein, or to any continuous portion of the sequences, from about 15-25 nucleotides in length up to and including the full length sequence, that one wishes to utilize as a probe or primer. The choice of probe and primer sequences may be governed by various

factors. For example, one may wish to employ primers from towards the termini of the total sequence.

Small polynucleotide segments or fragments may be readily prepared by, for example, directly synthesizing the fragment by chemical means, as is commonly practiced using an automated oligonucleotide synthesizer. Also, fragments may be obtained by application of nucleic acid reproduction technology, such as the PCR<sup>TM</sup> technology of U. S. Patent 4,683,202 (incorporated herein by reference), by introducing selected sequences into recombinant vectors for recombinant production, and by other recombinant DNA techniques generally known to those of skill in the art of molecular biology.

The nucleotide sequences of the invention may be used for their ability to selectively form duplex molecules with complementary stretches of the entire gene or gene fragments of interest. Depending on the application envisioned, one will typically desire to employ varying conditions of hybridization to achieve varying degrees of selectivity of probe towards target sequence. For applications requiring high selectivity, one will typically desire to employ relatively stringent conditions to form the hybrids, *e.g.*, one will select relatively low salt and/or high temperature conditions, such as provided by a salt concentration of from about 0.02 M to about 0.15 M salt at temperatures of from about 50°C to about 70°C. Such selective conditions tolerate little, if any, mismatch between the probe and the template or target strand, and would be particularly suitable for isolating related sequences.

Of course, for some applications, for example, where one desires to prepare mutants employing a mutant primer strand hybridized to an underlying template, less stringent (reduced stringency) hybridization conditions will typically be needed in order to allow formation of the heteroduplex. In these circumstances, one may desire to employ salt conditions such as those of from about 0.15 M to about 0.9 M salt, at temperatures ranging from about 20°C to about 55°C. Cross-hybridizing species can thereby be readily identified as positively hybridizing signals with respect to control hybridizations. In any case, it is generally appreciated that conditions can be rendered more stringent by the addition of increasing amounts of formamide, which serves to

destabilize the hybrid duplex in the same manner as increased temperature. Thus, hybridization conditions can be readily manipulated, and thus will generally be a method of choice depending on the desired results.

According to another embodiment of the present invention,  
5 polynucleotide compositions comprising antisense oligonucleotides are provided. Antisense oligonucleotides have been demonstrated to be effective and targeted inhibitors of protein synthesis, and, consequently, provide a therapeutic approach by which a disease can be treated by inhibiting the synthesis of proteins that contribute to the disease. The efficacy of antisense oligonucleotides for inhibiting protein synthesis  
10 is well established. For example, the synthesis of polygalacturonase and the muscarine type 2 acetylcholine receptor are inhibited by antisense oligonucleotides directed to their respective mRNA sequences (U. S. Patent 5,739,119 and U. S. Patent 5,759,829). Further, examples of antisense inhibition have been demonstrated with the nuclear protein cyclin, the multiple drug resistance gene (MDG1), ICAM-1, E-selectin, STK-1,  
15 striatal GABA<sub>A</sub> receptor and human EGF (Jaskulski *et al.*, Science. 1988 Jun 10;240(4858):1544-6; Vasanthakumar and Ahmed, Cancer Commun. 1989;1(4):225-32; Peris *et al.*, Brain Res Mol Brain Res. 1998 Jun 15;57(2):310-20; U. S. Patent 5,801,154; U.S. Patent 5,789,573; U. S. Patent 5,718,709 and U.S. Patent 5,610,288). Antisense constructs have also been described that inhibit and can be used to treat a  
20 variety of abnormal cellular proliferations, *e.g.* cancer (U. S. Patent 5,747,470; U. S. Patent 5,591,317 and U. S. Patent 5,783,683).

Therefore, in certain embodiments, the present invention provides oligonucleotide sequences that comprise all, or a portion of, any sequence that is capable of specifically binding to polynucleotide sequence described herein, or a  
25 complement thereof. In one embodiment, the antisense oligonucleotides comprise DNA or derivatives thereof. In another embodiment, the oligonucleotides comprise RNA or derivatives thereof. In a third embodiment, the oligonucleotides are modified DNAs comprising a phosphorothioated modified backbone. In a fourth embodiment, the oligonucleotide sequences comprise peptide nucleic acids or derivatives thereof. In  
30 each case, preferred compositions comprise a sequence region that is complementary,

and more preferably substantially-complementary, and even more preferably, completely complementary to one or more portions of polynucleotides disclosed herein. Selection of antisense compositions specific for a given gene sequence is based upon analysis of the chosen target sequence and determination of secondary structure,  $T_m$ ,  
5 binding energy, and relative stability. Antisense compositions may be selected based upon their relative inability to form dimers, hairpins, or other secondary structures that would reduce or prohibit specific binding to the target mRNA in a host cell. Highly preferred target regions of the mRNA, are those which are at or near the AUG translation initiation codon, and those sequences which are substantially complementary  
10 to 5' regions of the mRNA. These secondary structure analyses and target site selection considerations can be performed, for example, using v.4 of the OLIGO primer analysis software and/or the BLASTN 2.0.5 algorithm software (Altschul *et al.*, Nucleic Acids Res. 1997 Sep 1;25(17):3389-402).

The use of an antisense delivery method employing a short peptide  
15 vector, termed MPG (27 residues), is also contemplated. The MPG peptide contains a hydrophobic domain derived from the fusion sequence of HIV gp41 and a hydrophilic domain from the nuclear localization sequence of SV40 T-antigen (Morris *et al.*, Nucleic Acids Res. 1997 Jul 15;25(14):2730-6). It has been demonstrated that several molecules of the MPG peptide coat the antisense oligonucleotides and can be delivered  
20 into cultured mammalian cells in less than 1 hour with relatively high efficiency (90%). Further, the interaction with MPG strongly increases both the stability of the oligonucleotide to nuclease and the ability to cross the plasma membrane.

According to another embodiment of the invention, the polynucleotide compositions described herein are used in the design and preparation of ribozyme  
25 molecules for inhibiting expression of the tumor polypeptides and proteins of the present invention in tumor cells. Ribozymes are RNA-protein complexes that cleave nucleic acids in a site-specific fashion. Ribozymes have specific catalytic domains that possess endonuclease activity (Kim and Cech, Proc Natl Acad Sci U S A. 1987 Dec;84(24):8788-92; Forster and Symons, Cell. 1987 Apr 24;49(2):211-20). For  
30 example, a large number of ribozymes accelerate phosphoester transfer reactions with a

high degree of specificity, often cleaving only one of several phosphoesters in an oligonucleotide substrate (Cech *et al.*, Cell. 1981 Dec;27(3 Pt 2):487-96; Michel and Westhof, J Mol Biol. 1990 Dec 5;216(3):585-610; Reinhold-Hurek and Shub, Nature. 1992 May 14;357(6374):173-6). This specificity has been attributed to the requirement  
5 that the substrate bind via specific base-pairing interactions to the internal guide sequence ("IGS") of the ribozyme prior to chemical reaction.

Six basic varieties of naturally-occurring enzymatic RNAs are known presently. Each can catalyze the hydrolysis of RNA phosphodiester bonds *in trans* (and thus can cleave other RNA molecules) under physiological conditions. In general,  
10 enzymatic nucleic acids act by first binding to a target RNA. Such binding occurs through the target binding portion of a enzymatic nucleic acid which is held in close proximity to an enzymatic portion of the molecule that acts to cleave the target RNA. Thus, the enzymatic nucleic acid first recognizes and then binds a target RNA through complementary base-pairing, and once bound to the correct site, acts enzymatically to  
15 cut the target RNA. Strategic cleavage of such a target RNA will destroy its ability to direct synthesis of an encoded protein. After an enzymatic nucleic acid has bound and cleaved its RNA target, it is released from that RNA to search for another target and can repeatedly bind and cleave new targets.

The enzymatic nature of a ribozyme is advantageous over many  
20 technologies, such as antisense technology (where a nucleic acid molecule simply binds to a nucleic acid target to block its translation) since the concentration of ribozyme necessary to affect a therapeutic treatment is lower than that of an antisense oligonucleotide. This advantage reflects the ability of the ribozyme to act enzymatically. Thus, a single ribozyme molecule is able to cleave many molecules of  
25 target RNA. In addition, the ribozyme is a highly specific inhibitor, with the specificity of inhibition depending not only on the base pairing mechanism of binding to the target RNA, but also on the mechanism of target RNA cleavage. Single mismatches, or base-substitutions, near the site of cleavage can completely eliminate catalytic activity of a ribozyme. Similar mismatches in antisense molecules do not prevent their action  
30 (Woelf *et al.*, Proc Natl Acad Sci U S A. 1992 Aug 15;89(16):7305-9). Thus, the



specificity of action of a ribozyme is greater than that of an antisense oligonucleotide binding the same RNA site.

The enzymatic nucleic acid molecule may be formed in a hammerhead, hairpin, a hepatitis  $\delta$  virus, group I intron or RNaseP RNA (in association with an RNA  
5 guide sequence) or Neurospora VS RNA motif. Examples of hammerhead motifs are described by Rossi *et al.* Nucleic Acids Res. 1992 Sep 11;20(17):4559-65. Examples of hairpin motifs are described by Hampel *et al.* (Eur. Pat. Appl. Publ. No. EP 0360257), Hampel and Tritz, Biochemistry 1989 Jun 13;28(12):4929-33; Hampel *et al.*, Nucleic  
10 Acids Res. 1990 Jan 25;18(2):299-304 and U. S. Patent 5,631,359. An example of the hepatitis  $\delta$  virus motif is described by Perrotta and Been, Biochemistry. 1992 Dec 1;31(47):11843-52; an example of the RNaseP motif is described by Guerrier-Takada  
*et al.*, Cell. 1983 Dec;35(3 Pt 2):849-57; Neurospora VS RNA ribozyme motif is described by Collins (Saville and Collins, Cell. 1990 May 18;61(4):685-96; Saville and Collins, Proc Natl Acad Sci U S A. 1991 Oct 1;88(19):8826-30; Collins and Olive,  
15 Biochemistry. 1993 Mar 23;32(11):2795-9); and an example of the Group I intron is described in (U. S. Patent 4,987,071). All that is important in an enzymatic nucleic acid molecule of this invention is that it has a specific substrate binding site which is complementary to one or more of the target gene RNA regions, and that it have  
20 nucleotide sequences within or surrounding that substrate binding site which impart an RNA cleaving activity to the molecule. Thus the ribozyme constructs need not be limited to specific motifs mentioned herein.

Ribozymes may be designed as described in Int. Pat. Appl. Publ. No. WO 93/23569 and Int. Pat. Appl. Publ. No. WO 94/02595, each specifically incorporated herein by reference) and synthesized to be tested *in vitro* and *in vivo*, as  
25 described. Such ribozymes can also be optimized for delivery. While specific examples are provided, those in the art will recognize that equivalent RNA targets in other species can be utilized when necessary.

Ribozyme activity can be optimized by altering the length of the ribozyme binding arms, or chemically synthesizing ribozymes with modifications that  
30 prevent their degradation by serum ribonucleases (see *e.g.*, Int. Pat. Appl. Publ. No. WO

92/07065; Int. Pat. Appl. Publ. No. WO 93/15187; Int. Pat. Appl. Publ. No. WO 91/03162; Eur. Pat. Appl. Publ. No. 92110298.4; U. S. Patent 5,334,711; and Int. Pat. Appl. Publ. No. WO 94/13688, which describe various chemical modifications that can be made to the sugar moieties of enzymatic RNA molecules), modifications which enhance their efficacy in cells, and removal of stem II bases to shorten RNA synthesis times and reduce chemical requirements.

Sullivan *et al.* (Int. Pat. Appl. Publ. No. WO 94/02595) describes the general methods for delivery of enzymatic RNA molecules. Ribozymes may be administered to cells by a variety of methods known to those familiar to the art, including, but not restricted to, encapsulation in liposomes, by iontophoresis, or by incorporation into other vehicles, such as hydrogels, cyclodextrins, biodegradable nanocapsules, and bioadhesive microspheres. For some indications, ribozymes may be directly delivered *ex vivo* to cells or tissues with or without the aforementioned vehicles. Alternatively, the RNA/vehicle combination may be locally delivered by direct inhalation, by direct injection or by use of a catheter, infusion pump or stent. Other routes of delivery include, but are not limited to, intravascular, intramuscular, subcutaneous or joint injection, aerosol inhalation, oral (tablet or pill form), topical, systemic, ocular, intraperitoneal and/or intrathecal delivery. More detailed descriptions of ribozyme delivery and administration are provided in Int. Pat. Appl. Publ. No. WO 94/02595 and Int. Pat. Appl. Publ. No. WO 93/23569, each specifically incorporated herein by reference.

Another means of accumulating high concentrations of a ribozyme(s) within cells is to incorporate the ribozyme-encoding sequences into a DNA expression vector. Transcription of the ribozyme sequences are driven from a promoter for eukaryotic RNA polymerase I (pol I), RNA polymerase II (pol II), or RNA polymerase III (pol III). Transcripts from pol II or pol III promoters will be expressed at high levels in all cells; the levels of a given pol II promoter in a given cell type will depend on the nature of the gene regulatory sequences (enhancers, silencers, *etc.*) present nearby. Prokaryotic RNA polymerase promoters may also be used, providing that the prokaryotic RNA polymerase enzyme is expressed in the appropriate cells. Ribozymes

expressed from such promoters have been shown to function in mammalian cells. Such transcription units can be incorporated into a variety of vectors for introduction into mammalian cells, including but not restricted to, plasmid DNA vectors, viral DNA vectors (such as adenovirus or adeno-associated vectors), or viral RNA vectors (such as  
5 retroviral, semliki forest virus, sindbis virus vectors).

In another embodiment of the invention, peptide nucleic acids (PNAs) compositions are provided. PNA is a DNA mimic in which the nucleobases are attached to a pseudopeptide backbone (Good and Nielsen, *Antisense Nucleic Acid Drug Dev.* 1997 7(4) 431-37). PNA is able to be utilized in a number methods that  
10 traditionally have used RNA or DNA. Often PNA sequences perform better in techniques than the corresponding RNA or DNA sequences and have utilities that are not inherent to RNA or DNA. A review of PNA including methods of making, characteristics of, and methods of using, is provided by Corey (*Trends Biotechnol* 1997 Jun;15(6):224-9). As such, in certain embodiments, one may prepare PNA sequences  
15 that are complementary to one or more portions of the ACE mRNA sequence, and such PNA compositions may be used to regulate, alter, decrease, or reduce the translation of ACE-specific mRNA, and thereby alter the level of ACE activity in a host cell to which such PNA compositions have been administered.

PNAs have 2-aminoethyl-glycine linkages replacing the normal  
20 phosphodiester backbone of DNA (Nielsen *et al.*, *Science* 1991 Dec 6;254(5037):1497-500; Hanvey *et al.*, *Science*. 1992 Nov 27;258(5087):1481-5; Hyrup and Nielsen, *Bioorg Med Chem.* 1996 Jan;4(1):5-23). This chemistry has three important consequences: firstly, in contrast to DNA or phosphorothioate oligonucleotides, PNAs are neutral molecules; secondly, PNAs are achiral, which avoids the need to develop a  
25 stereoselective synthesis; and thirdly, PNA synthesis uses standard Boc or Fmoc protocols for solid-phase peptide synthesis, although other methods, including a modified Merrifield method, have been used.

PNA monomers or ready-made oligomers are commercially available from PerSeptive Biosystems (Framingham, MA). PNA syntheses by either Boc or  
30 Fmoc protocols are straightforward using manual or automated protocols (Norton *et al.*,

Bioorg Med Chem. 1995 Apr;3(4):437-45). The manual protocol lends itself to the production of chemically modified PNAs or the simultaneous synthesis of families of closely related PNAs.

As with peptide synthesis, the success of a particular PNA synthesis will  
5 depend on the properties of the chosen sequence. For example, while in theory PNAs can incorporate any combination of nucleotide bases, the presence of adjacent purines can lead to deletions of one or more residues in the product. In expectation of this difficulty, it is suggested that, in producing PNAs with adjacent purines, one should repeat the coupling of residues likely to be added inefficiently. This should be followed  
10 by the purification of PNAs by reverse-phase high-pressure liquid chromatography, providing yields and purity of product similar to those observed during the synthesis of peptides.

Modifications of PNAs for a given application may be accomplished by coupling amino acids during solid-phase synthesis or by attaching compounds that  
15 contain a carboxylic acid group to the exposed N-terminal amine. Alternatively, PNAs can be modified after synthesis by coupling to an introduced lysine or cysteine. The ease with which PNAs can be modified facilitates optimization for better solubility or for specific functional requirements. Once synthesized, the identity of PNAs and their derivatives can be confirmed by mass spectrometry. Several studies have made and  
20 utilized modifications of PNAs (for example, Norton *et al.*, Bioorg Med Chem. 1995 Apr;3(4):437-45; Petersen *et al.*, J Pept Sci. 1995 May-Jun;1(3):175-83; Orum *et al.*, Biotechniques. 1995 Sep;19(3):472-80; Footer *et al.*, Biochemistry. 1996 Aug 20;35(33):10673-9; Griffith *et al.*, Nucleic Acids Res. 1995 Aug 11;23(15):3003-8; Pardridge *et al.*, Proc Natl Acad Sci U S A. 1995 Jun 6;92(12):5592-6; Boffa *et al.*,  
25 Proc Natl Acad Sci U S A. 1995 Mar 14;92(6):1901-5; Gambacorti-Passerini *et al.*, Blood. 1996 Aug 15;88(4):1411-7; Armitage *et al.*, Proc Natl Acad Sci U S A. 1997 Nov 11;94(23):12320-5; Seeger *et al.*, Biotechniques. 1997 Sep;23(3):512-7). U.S. Patent No. 5,700,922 discusses PNA-DNA-PNA chimeric molecules and their uses in diagnostics, modulating protein in organisms, and treatment of conditions susceptible to  
30 therapeutics.

Methods of characterizing the antisense binding properties of PNAs are discussed in Rose (Anal Chem. 1993 Dec 15;65(24):3545-9) and Jensen *et al.* (Biochemistry. 1997 Apr 22;36(16):5072-7). Rose uses capillary gel electrophoresis to determine binding of PNAs to their complementary oligonucleotide, measuring the  
5 relative binding kinetics and stoichiometry. Similar types of measurements were made by Jensen *et al.* using BIAcore™ technology.

Other applications of PNAs that have been described and will be apparent to the skilled artisan include use in DNA strand invasion, antisense inhibition, mutational analysis, enhancers of transcription, nucleic acid purification, isolation of  
10 transcriptionally active genes, blocking of transcription factor binding, genome cleavage, biosensors, *in situ* hybridization, and the like.

#### Polynucleotide Identification, Characterization and Expression

Polynucleotide compositions of the present invention may be identified, prepared and/or manipulated using any of a variety of well established techniques (see  
15 generally, Sambrook et al., *Molecular Cloning: A Laboratory Manual*, Cold Spring Harbor Laboratories, Cold Spring Harbor, NY, 1989, and other like references). For example, a polynucleotide may be identified, as described in more detail below, by screening a microarray of cDNAs for tumor-associated expression (*i.e.*, expression that is at least two fold greater in a tumor than in normal tissue, as determined using a  
20 representative assay provided herein). Such screens may be performed, for example, using the microarray technology of Affymetrix, Inc. (Santa Clara, CA) according to the manufacturer's instructions (and essentially as described by Schena et al., *Proc. Natl. Acad. Sci. USA* 93:10614-10619, 1996 and Heller et al., *Proc. Natl. Acad. Sci. USA* 94:2150-2155, 1997). Alternatively, polynucleotides may be amplified from cDNA  
25 prepared from cells expressing the proteins described herein, such as tumor cells.

Many template dependent processes are available to amplify a target sequences of interest present in a sample. One of the best known amplification methods is the polymerase chain reaction (PCR™) which is described in detail in U.S. Patent Nos. 4,683,195, 4,683,202 and 4,800,159, each of which is incorporated herein by

reference in its entirety. Briefly, in PCR™, two primer sequences are prepared which are complementary to regions on opposite complementary strands of the target sequence. An excess of deoxynucleoside triphosphates is added to a reaction mixture along with a DNA polymerase (*e.g.*, *Taq* polymerase). If the target sequence is present  
5 in a sample, the primers will bind to the target and the polymerase will cause the primers to be extended along the target sequence by adding on nucleotides. By raising and lowering the temperature of the reaction mixture, the extended primers will dissociate from the target to form reaction products, excess primers will bind to the target and to the reaction product and the process is repeated. Preferably reverse  
10 transcription and PCR™ amplification procedure may be performed in order to quantify the amount of mRNA amplified. Polymerase chain reaction methodologies are well known in the art.

Any of a number of other template dependent processes, many of which are variations of the PCR™ amplification technique, are readily known and available in  
15 the art. Illustratively, some such methods include the ligase chain reaction (referred to as LCR), described, for example, in Eur. Pat. Appl. Publ. No. 320,308 and U.S. Patent No. 4,883,750; Qbeta Replicase, described in PCT Intl. Pat. Appl. Publ. No. PCT/US87/00880; Strand Displacement Amplification (SDA) and Repair Chain Reaction (RCR). Still other amplification methods are described in Great Britain Pat.  
20 Appl. No. 2 202 328, and in PCT Intl. Pat. Appl. Publ. No. PCT/US89/01025. Other nucleic acid amplification procedures include transcription-based amplification systems (TAS) (PCT Intl. Pat. Appl. Publ. No. WO 88/10315), including nucleic acid sequence based amplification (NASBA) and 3SR. Eur. Pat. Appl. Publ. No. 329,822 describes a nucleic acid amplification process involving cyclically synthesizing single-stranded  
25 RNA ("ssRNA"), ssDNA, and double-stranded DNA (dsDNA). PCT Intl. Pat. Appl. Publ. No. WO 89/06700 describes a nucleic acid sequence amplification scheme based on the hybridization of a promoter/primer sequence to a target single-stranded DNA ("ssDNA") followed by transcription of many RNA copies of the sequence. Other amplification methods such as "RACE" (Frohman, 1990), and "one-sided PCR" (Ohara,  
30 1989) are also well-known to those of skill in the art.

An amplified portion of a polynucleotide of the present invention may be used to isolate a full length gene from a suitable library (e.g., a tumor cDNA library) using well known techniques. Within such techniques, a library (cDNA or genomic) is screened using one or more polynucleotide probes or primers suitable for amplification.

- 5 Preferably, a library is size-selected to include larger molecules. Random primed libraries may also be preferred for identifying 5' and upstream regions of genes. Genomic libraries are preferred for obtaining introns and extending 5' sequences.

For hybridization techniques, a partial sequence may be labeled (e.g., by nick-translation or end-labeling with  $^{32}\text{P}$ ) using well known techniques. A bacterial or  
10 bacteriophage library is then generally screened by hybridizing filters containing denatured bacterial colonies (or lawns containing phage plaques) with the labeled probe (see Sambrook et al., *Molecular Cloning: A Laboratory Manual*, Cold Spring Harbor Laboratories, Cold Spring Harbor, NY, 1989). Hybridizing colonies or plaques are selected and expanded, and the DNA is isolated for further analysis. cDNA clones may  
15 be analyzed to determine the amount of additional sequence by, for example, PCR using a primer from the partial sequence and a primer from the vector. Restriction maps and partial sequences may be generated to identify one or more overlapping clones. The complete sequence may then be determined using standard techniques, which may involve generating a series of deletion clones. The resulting overlapping sequences can  
20 then assembled into a single contiguous sequence. A full length cDNA molecule can be generated by ligating suitable fragments, using well known techniques.

Alternatively, amplification techniques, such as those described above, can be useful for obtaining a full length coding sequence from a partial cDNA sequence. One such amplification technique is inverse PCR (see Triglia et al., *Nucl. Acids Res.*  
25 16:8186, 1988), which uses restriction enzymes to generate a fragment in the known region of the gene. The fragment is then circularized by intramolecular ligation and used as a template for PCR with divergent primers derived from the known region. Within an alternative approach, sequences adjacent to a partial sequence may be retrieved by amplification with a primer to a linker sequence and a primer specific to a  
30 known region. The amplified sequences are typically subjected to a second round of

amplification with the same linker primer and a second primer specific to the known region. A variation on this procedure, which employs two primers that initiate extension in opposite directions from the known sequence, is described in WO 96/38591. Another such technique is known as "rapid amplification of cDNA ends" or RACE. This technique involves the use of an internal primer and an external primer, which hybridizes to a polyA region or vector sequence, to identify sequences that are 5' and 3' of a known sequence. Additional techniques include capture PCR (Lagerstrom et al., *PCR Methods Applic. 1*:111-19, 1991) and walking PCR (Parker et al., *Nucl. Acids. Res. 19*:3055-60, 1991). Other methods employing amplification may also be employed to obtain a full length cDNA sequence.

In certain instances, it is possible to obtain a full length cDNA sequence by analysis of sequences provided in an expressed sequence tag (EST) database, such as that available from GenBank. Searches for overlapping ESTs may generally be performed using well known programs (e.g., NCBI BLAST searches), and such ESTs may be used to generate a contiguous full length sequence. Full length DNA sequences may also be obtained by analysis of genomic fragments.

In other embodiments of the invention, polynucleotide sequences or fragments thereof which encode polypeptides of the invention, or fusion proteins or functional equivalents thereof, may be used in recombinant DNA molecules to direct expression of a polypeptide in appropriate host cells. Due to the inherent degeneracy of the genetic code, other DNA sequences that encode substantially the same or a functionally equivalent amino acid sequence may be produced and these sequences may be used to clone and express a given polypeptide.

As will be understood by those of skill in the art, it may be advantageous in some instances to produce polypeptide-encoding nucleotide sequences possessing non-naturally occurring codons. For example, codons preferred by a particular prokaryotic or eukaryotic host can be selected to increase the rate of protein expression or to produce a recombinant RNA transcript having desirable properties, such as a half-life which is longer than that of a transcript generated from the naturally occurring sequence.



Moreover, the polynucleotide sequences of the present invention can be engineered using methods generally known in the art in order to alter polypeptide encoding sequences for a variety of reasons, including but not limited to, alterations which modify the cloning, processing, and/or expression of the gene product. For example, DNA shuffling by random fragmentation and PCR reassembly of gene fragments and synthetic oligonucleotides may be used to engineer the nucleotide sequences. In addition, site-directed mutagenesis may be used to insert new restriction sites, alter glycosylation patterns, change codon preference, produce splice variants, or introduce mutations, and so forth.

In another embodiment of the invention, natural, modified, or recombinant nucleic acid sequences may be ligated to a heterologous sequence to encode a fusion protein. For example, to screen peptide libraries for inhibitors of polypeptide activity, it may be useful to encode a chimeric protein that can be recognized by a commercially available antibody. A fusion protein may also be engineered to contain a cleavage site located between the polypeptide-encoding sequence and the heterologous protein sequence, so that the polypeptide may be cleaved and purified away from the heterologous moiety.

Sequences encoding a desired polypeptide may be synthesized, in whole or in part, using chemical methods well known in the art (see Caruthers, M. H. et al. (1980) *Nucl. Acids Res. Symp. Ser.* 215-223, Horn, T. et al. (1980) *Nucl. Acids Res. Symp. Ser.* 225-232). Alternatively, the protein itself may be produced using chemical methods to synthesize the amino acid sequence of a polypeptide, or a portion thereof. For example, peptide synthesis can be performed using various solid-phase techniques (Roberge, J. Y. et al. (1995) *Science* 269:202-204) and automated synthesis may be achieved, for example, using the ABI 431A Peptide Synthesizer (Perkin Elmer, Palo Alto, CA).

A newly synthesized peptide may be substantially purified by preparative high performance liquid chromatography (e.g., Creighton, T. (1983) *Proteins, Structures and Molecular Principles*, WH Freeman and Co., New York, N.Y.) or other comparable techniques available in the art. The composition of the synthetic peptides may be

confirmed by amino acid analysis or sequencing (*e.g.*, the Edman degradation procedure). Additionally, the amino acid sequence of a polypeptide, or any part thereof, may be altered during direct synthesis and/or combined using chemical methods with sequences from other proteins, or any part thereof, to produce a variant polypeptide.

5           In order to express a desired polypeptide, the nucleotide sequences encoding the polypeptide, or functional equivalents, may be inserted into appropriate expression vector, *i.e.*, a vector which contains the necessary elements for the transcription and translation of the inserted coding sequence. Methods which are well known to those skilled in the art may be used to construct expression vectors containing  
10 sequences encoding a polypeptide of interest and appropriate transcriptional and translational control elements. These methods include *in vitro* recombinant DNA techniques, synthetic techniques, and *in vivo* genetic recombination. Such techniques are described, for example, in Sambrook, J. et al. (1989) Molecular Cloning, A Laboratory Manual, Cold Spring Harbor Press, Plainview, N.Y., and Ausubel, F. M. et al. (1989) Current Protocols in Molecular Biology, John Wiley & Sons, New York.  
15 N.Y.

A variety of expression vector/host systems may be utilized to contain and express polynucleotide sequences. These include, but are not limited to, microorganisms such as bacteria transformed with recombinant bacteriophage, plasmid,  
20 or cosmid DNA expression vectors; yeast transformed with yeast expression vectors; insect cell systems infected with virus expression vectors (*e.g.*, baculovirus); plant cell systems transformed with virus expression vectors (*e.g.*, cauliflower mosaic virus, CaMV; tobacco mosaic virus, TMV) or with bacterial expression vectors (*e.g.*, Ti or pBR322 plasmids); or animal cell systems.

25           The "control elements" or "regulatory sequences" present in an expression vector are those non-translated regions of the vector--enhancers, promoters, 5' and 3' untranslated regions--which interact with host cellular proteins to carry out transcription and translation. Such elements may vary in their strength and specificity. Depending on the vector system and host utilized, any number of suitable transcription  
30 and translation elements, including constitutive and inducible promoters, may be used.

For example, when cloning in bacterial systems, inducible promoters such as the hybrid lacZ promoter of the PBLUESCRIPT phagemid (Stratagene, La Jolla, Calif.) or PSPORT1 plasmid (Gibco BRL, Gaithersburg, MD) and the like may be used. In mammalian cell systems, promoters from mammalian genes or from mammalian viruses  
5 are generally preferred. If it is necessary to generate a cell line that contains multiple copies of the sequence encoding a polypeptide, vectors based on SV40 or EBV may be advantageously used with an appropriate selectable marker.

In bacterial systems, any of a number of expression vectors may be selected depending upon the use intended for the expressed polypeptide. For example,  
10 when large quantities are needed, for example for the induction of antibodies, vectors which direct high level expression of fusion proteins that are readily purified may be used. Such vectors include, but are not limited to, the multifunctional *E. coli* cloning and expression vectors such as BLUESCRIPT (Stratagene), in which the sequence encoding the polypeptide of interest may be ligated into the vector in frame with  
15 sequences for the amino-terminal Met and the subsequent 7 residues of .beta.-galactosidase so that a hybrid protein is produced; pIN vectors (Van Heeke, G. and S. M. Schuster (1989) *J. Biol. Chem.* 264:5503-5509); and the like. pGEX Vectors (Promega, Madison, Wis.) may also be used to express foreign polypeptides as fusion proteins with glutathione S-transferase (GST). In general, such fusion proteins are  
20 soluble and can easily be purified from lysed cells by adsorption to glutathione-agarose beads followed by elution in the presence of free glutathione. Proteins made in such systems may be designed to include heparin, thrombin, or factor XA protease cleavage sites so that the cloned polypeptide of interest can be released from the GST moiety at will.

25 In the yeast, *Saccharomyces cerevisiae*, a number of vectors containing constitutive or inducible promoters such as alpha factor, alcohol oxidase, and PGH may be used. For reviews, see Ausubel et al. (supra) and Grant et al. (1987) *Methods Enzymol.* 153:516-544.

In cases where plant expression vectors are used, the expression of  
30 sequences encoding polypeptides may be driven by any of a number of promoters. For

example, viral promoters such as the 35S and 19S promoters of CaMV may be used alone or in combination with the omega leader sequence from TMV (Takamatsu, N. (1987) *EMBO J.* 6:307-311. Alternatively, plant promoters such as the small subunit of RUBISCO or heat shock promoters may be used (Coruzzi, G. et al. (1984) *EMBO J.* 3:1671-1680; Broglie, R. et al. (1984) *Science* 224:838-843; and Winter, J. et al. (1991) *Results Probl. Cell Differ.* 17:85-105). These constructs can be introduced into plant cells by direct DNA transformation or pathogen-mediated transfection. Such techniques are described in a number of generally available reviews (see, for example, Hobbs, S. or Murry, L. E. in McGraw Hill Yearbook of Science and Technology (1992) McGraw Hill, New York, N.Y.; pp. 191-196).

An insect system may also be used to express a polypeptide of interest. For example, in one such system, Autographa californica nuclear polyhedrosis virus (AcNPV) is used as a vector to express foreign genes in *Spodoptera frugiperda* cells or in *Trichoplusia* larvae. The sequences encoding the polypeptide may be cloned into a non-essential region of the virus, such as the polyhedrin gene, and placed under control of the polyhedrin promoter. Successful insertion of the polypeptide-encoding sequence will render the polyhedrin gene inactive and produce recombinant virus lacking coat protein. The recombinant viruses may then be used to infect, for example, *S. frugiperda* cells or *Trichoplusia* larvae in which the polypeptide of interest may be expressed (Engelhard, E. K. et al. (1994) *Proc. Natl. Acad. Sci.* 91:3224-3227).

In mammalian host cells, a number of viral-based expression systems are generally available. For example, in cases where an adenovirus is used as an expression vector, sequences encoding a polypeptide of interest may be ligated into an adenovirus transcription/translation complex consisting of the late promoter and tripartite leader sequence. Insertion in a non-essential E1 or E3 region of the viral genome may be used to obtain a viable virus which is capable of expressing the polypeptide in infected host cells (Logan, J. and Shenk, T. (1984) *Proc. Natl. Acad. Sci.* 81:3655-3659). In addition, transcription enhancers, such as the Rous sarcoma virus (RSV) enhancer, may be used to increase expression in mammalian host cells.

Specific initiation signals may also be used to achieve more efficient translation of sequences encoding a polypeptide of interest. Such signals include the ATG initiation codon and adjacent sequences. In cases where sequences encoding the polypeptide, its initiation codon, and upstream sequences are inserted into the appropriate expression vector, no additional transcriptional or translational control signals may be needed. However, in cases where only coding sequence, or a portion thereof, is inserted, exogenous translational control signals including the ATG initiation codon should be provided. Furthermore, the initiation codon should be in the correct reading frame to ensure translation of the entire insert. Exogenous translational elements and initiation codons may be of various origins, both natural and synthetic. The efficiency of expression may be enhanced by the inclusion of enhancers which are appropriate for the particular cell system which is used, such as those described in the literature (Scharf, D. et al. (1994) *Results Probl. Cell Differ.* 20:125-162).

In addition, a host cell strain may be chosen for its ability to modulate the expression of the inserted sequences or to process the expressed protein in the desired fashion. Such modifications of the polypeptide include, but are not limited to, acetylation, carboxylation, glycosylation, phosphorylation, lipidation, and acylation. Post-translational processing which cleaves a "prepro" form of the protein may also be used to facilitate correct insertion, folding and/or function. Different host cells such as CHO, COS, HeLa, MDCK, HEK293, and WI38, which have specific cellular machinery and characteristic mechanisms for such post-translational activities, may be chosen to ensure the correct modification and processing of the foreign protein.

For long-term, high-yield production of recombinant proteins, stable expression is generally preferred. For example, cell lines which stably express a polynucleotide of interest may be transformed using expression vectors which may contain viral origins of replication and/or endogenous expression elements and a selectable marker gene on the same or on a separate vector. Following the introduction of the vector, cells may be allowed to grow for 1-2 days in an enriched media before they are switched to selective media. The purpose of the selectable marker is to confer resistance to selection, and its presence allows growth and recovery of cells which

successfully express the introduced sequences. Resistant clones of stably transformed cells may be proliferated using tissue culture techniques appropriate to the cell type.

Any number of selection systems may be used to recover transformed cell lines. These include, but are not limited to, the herpes simplex virus thymidine kinase (Wigler, M. et al. (1977) *Cell* 11:223-32) and adenine phosphoribosyltransferase (Lowy, I. et al. (1990) *Cell* 22:817-23) genes which can be employed in tk.sup.- or aprt.sup.- cells, respectively. Also, antimetabolite, antibiotic or herbicide resistance can be used as the basis for selection; for example, dhfr which confers resistance to methotrexate (Wigler, M. et al. (1980) *Proc. Natl. Acad. Sci.* 77:3567-70); npt, which confers resistance to the aminoglycosides, neomycin and G-418 (Colbere-Garapin, F. et al (1981) *J. Mol. Biol.* 150:1-14); and als or pat, which confer resistance to chlorsulfuron and phosphinotricin acetyltransferase, respectively (Murry, *supra*). Additional selectable genes have been described, for example, trpB, which allows cells to utilize indole in place of tryptophan, or hisD, which allows cells to utilize histinol in place of histidine (Hartman, S. C. and R. C. Mulligan (1988) *Proc. Natl. Acad. Sci.* 85:8047-51). The use of visible markers has gained popularity with such markers as anthocyanins, beta-glucuronidase and its substrate GUS, and luciferase and its substrate luciferin, being widely used not only to identify transformants, but also to quantify the amount of transient or stable protein expression attributable to a specific vector system (Rhodes, C. A. et al. (1995) *Methods Mol. Biol.* 55:121-131).

Although the presence/absence of marker gene expression suggests that the gene of interest is also present, its presence and expression may need to be confirmed. For example, if the sequence encoding a polypeptide is inserted within a marker gene sequence, recombinant cells containing sequences can be identified by the absence of marker gene function. Alternatively, a marker gene can be placed in tandem with a polypeptide-encoding sequence under the control of a single promoter. Expression of the marker gene in response to induction or selection usually indicates expression of the tandem gene as well.

Alternatively, host cells that contain and express a desired polynucleotide sequence may be identified by a variety of procedures known to those of

skill in the art. These procedures include, but are not limited to, DNA-DNA or DNA-RNA hybridizations and protein bioassay or immunoassay techniques which include, for example, membrane, solution, or chip based technologies for the detection and/or quantification of nucleic acid or protein.

5           A variety of protocols for detecting and measuring the expression of polynucleotide-encoded products, using either polyclonal or monoclonal antibodies specific for the product are known in the art. Examples include enzyme-linked immunosorbent assay (ELISA), radioimmunoassay (RIA), and fluorescence activated cell sorting (FACS). A two-site, monoclonal-based immunoassay utilizing monoclonal  
10 antibodies reactive to two non-interfering epitopes on a given polypeptide may be preferred for some applications, but a competitive binding assay may also be employed. These and other assays are described, among other places, in Hampton, R. et al. (1990; *Serological Methods, a Laboratory Manual*, APS Press, St Paul, Minn.) and Maddox, D. E. et al. (1983; *J. Exp. Med.* 158:1211-1216).

15           A wide variety of labels and conjugation techniques are known by those skilled in the art and may be used in various nucleic acid and amino acid assays. Means for producing labeled hybridization or PCR probes for detecting sequences related to polynucleotides include oligolabeling, nick translation, end-labeling or PCR amplification using a labeled nucleotide. Alternatively, the sequences, or any portions  
20 thereof may be cloned into a vector for the production of an mRNA probe. Such vectors are known in the art, are commercially available, and may be used to synthesize RNA probes in vitro by addition of an appropriate RNA polymerase such as T7, T3, or SP6 and labeled nucleotides. These procedures may be conducted using a variety of commercially available kits. Suitable reporter molecules or labels, which may be used  
25 include radionuclides, enzymes, fluorescent, chemiluminescent, or chromogenic agents as well as substrates, cofactors, inhibitors, magnetic particles, and the like.

          Host cells transformed with a polynucleotide sequence of interest may be cultured under conditions suitable for the expression and recovery of the protein from cell culture. The protein produced by a recombinant cell may be secreted or contained  
30 intracellularly depending on the sequence and/or the vector used. As will be understood

by those of skill in the art, expression vectors containing polynucleotides of the invention may be designed to contain signal sequences which direct secretion of the encoded polypeptide through a prokaryotic or eukaryotic cell membrane. Other recombinant constructions may be used to join sequences encoding a polypeptide of interest to nucleotide sequence encoding a polypeptide domain which will facilitate purification of soluble proteins. Such purification facilitating domains include, but are not limited to, metal chelating peptides such as histidine-tryptophan modules that allow purification on immobilized metals, protein A domains that allow purification on immobilized immunoglobulin, and the domain utilized in the FLAGS extension/affinity purification system (Immunex Corp., Seattle, Wash.). The inclusion of cleavable linker sequences such as those specific for Factor XA or enterokinase (Invitrogen, San Diego, Calif.) between the purification domain and the encoded polypeptide may be used to facilitate purification. One such expression vector provides for expression of a fusion protein containing a polypeptide of interest and a nucleic acid encoding 6 histidine residues preceding a thioredoxin or an enterokinase cleavage site. The histidine residues facilitate purification on IMIAC (immobilized metal ion affinity chromatography) as described in Porath, J. et al. (1992, *Prot. Exp. Purif.* 3:263-281) while the enterokinase cleavage site provides a means for purifying the desired polypeptide from the fusion protein. A discussion of vectors which contain fusion proteins is provided in Kroll, D. J. et al. (1993; *DNA Cell Biol.* 12:441-453).

In addition to recombinant production methods, polypeptides of the invention, and fragments thereof, may be produced by direct peptide synthesis using solid-phase techniques (Merrifield J. (1963) *J. Am. Chem. Soc.* 85:2149-2154). Protein synthesis may be performed using manual techniques or by automation. Automated synthesis may be achieved, for example, using Applied Biosystems 431A Peptide Synthesizer (Perkin Elmer). Alternatively, various fragments may be chemically synthesized separately and combined using chemical methods to produce the full length molecule.



Antibody Compositions, Fragments Thereof and Other Binding Agents

According to another aspect, the present invention further provides binding agents, such as antibodies and antigen-binding fragments thereof, that exhibit immunological binding to a tumor polypeptide disclosed herein, or to a portion, variant  
5 or derivative thereof. An antibody, or antigen-binding fragment thereof, is said to "specifically bind," "immunologically bind," and/or is "immunologically reactive" to a polypeptide of the invention if it reacts at a detectable level (within, for example, an ELISA assay) with the polypeptide, and does not react detectably with unrelated polypeptides under similar conditions.

10 Immunological binding, as used in this context, generally refers to the non-covalent interactions of the type which occur between an immunoglobulin molecule and an antigen for which the immunoglobulin is specific. The strength, or affinity of immunological binding interactions can be expressed in terms of the dissociation constant ( $K_d$ ) of the interaction, wherein a smaller  $K_d$  represents a greater  
15 affinity. Immunological binding properties of selected polypeptides can be quantified using methods well known in the art. One such method entails measuring the rates of antigen-binding site/antigen complex formation and dissociation, wherein those rates depend on the concentrations of the complex partners, the affinity of the interaction, and on geometric parameters that equally influence the rate in both directions. Thus, both  
20 the "on rate constant" ( $K_{on}$ ) and the "off rate constant" ( $K_{off}$ ) can be determined by calculation of the concentrations and the actual rates of association and dissociation. The ratio of  $K_{off}/K_{on}$  enables cancellation of all parameters not related to affinity, and is thus equal to the dissociation constant  $K_d$ . See, generally, Davies et al. (1990) Annual Rev. Biochem. 59:439-473.

25 An "antigen-binding site," or "binding portion" of an antibody refers to the part of the immunoglobulin molecule that participates in antigen binding. The antigen binding site is formed by amino acid residues of the N-terminal variable ("V") regions of the heavy ("H") and light ("L") chains. Three highly divergent stretches within the V regions of the heavy and light chains are referred to as "hypervariable  
30 regions" which are interposed between more conserved flanking stretches known as

"framework regions," or "FRs". Thus the term "FR" refers to amino acid sequences which are naturally found between and adjacent to hypervariable regions in immunoglobulins. In an antibody molecule, the three hypervariable regions of a light chain and the three hypervariable regions of a heavy chain are disposed relative to each other in three dimensional space to form an antigen-binding surface. The antigen-binding surface is complementary to the three-dimensional surface of a bound antigen, and the three hypervariable regions of each of the heavy and light chains are referred to as "complementarity-determining regions," or "CDRs."

Binding agents may be further capable of differentiating between patients with and without a cancer, such as prostate cancer, using the representative assays provided herein. For example, antibodies or other binding agents that bind to a tumor protein will preferably generate a signal indicating the presence of a cancer in at least about 20% of patients with the disease, more preferably at least about 30% of patients. Alternatively, or in addition, the antibody will generate a negative signal indicating the absence of the disease in at least about 90% of individuals without the cancer. To determine whether a binding agent satisfies this requirement, biological samples (e.g., blood, sera, sputum, urine and/or tumor biopsies) from patients with and without a cancer (as determined using standard clinical tests) may be assayed as described herein for the presence of polypeptides that bind to the binding agent. Preferably, a statistically significant number of samples with and without the disease will be assayed. Each binding agent should satisfy the above criteria; however, those of ordinary skill in the art will recognize that binding agents may be used in combination to improve sensitivity.

Any agent that satisfies the above requirements may be a binding agent. For example, a binding agent may be a ribosome, with or without a peptide component, an RNA molecule or a polypeptide. In a preferred embodiment, a binding agent is an antibody or an antigen-binding fragment thereof. Antibodies may be prepared by any of a variety of techniques known to those of ordinary skill in the art. See, e.g., Harlow and Lane, *Antibodies: A Laboratory Manual*, Cold Spring Harbor Laboratory, 1988. In general, antibodies can be produced by cell culture techniques, including the generation

of monoclonal antibodies as described herein, or via transfection of antibody genes into suitable bacterial or mammalian cell hosts, in order to allow for the production of recombinant antibodies. In one technique, an immunogen comprising the polypeptide is initially injected into any of a wide variety of mammals (*e.g.*, mice, rats, rabbits, sheep or goats). In this step, the polypeptides of this invention may serve as the immunogen without modification. Alternatively, particularly for relatively short polypeptides, a superior immune response may be elicited if the polypeptide is joined to a carrier protein, such as bovine serum albumin or keyhole limpet hemocyanin. The immunogen is injected into the animal host, preferably according to a predetermined schedule incorporating one or more booster immunizations, and the animals are bled periodically. Polyclonal antibodies specific for the polypeptide may then be purified from such antisera by, for example, affinity chromatography using the polypeptide coupled to a suitable solid support.

Monoclonal antibodies specific for an antigenic polypeptide of interest may be prepared, for example, using the technique of Kohler and Milstein, *Eur. J. Immunol.* 6:511-519, 1976, and improvements thereto. Briefly, these methods involve the preparation of immortal cell lines capable of producing antibodies having the desired specificity (*i.e.*, reactivity with the polypeptide of interest). Such cell lines may be produced, for example, from spleen cells obtained from an animal immunized as described above. The spleen cells are then immortalized by, for example, fusion with a myeloma cell fusion partner, preferably one that is syngeneic with the immunized animal. A variety of fusion techniques may be employed. For example, the spleen cells and myeloma cells may be combined with a nonionic detergent for a few minutes and then plated at low density on a selective medium that supports the growth of hybrid cells, but not myeloma cells. A preferred selection technique uses HAT (hypoxanthine, aminopterin, thymidine) selection. After a sufficient time, usually about 1 to 2 weeks, colonies of hybrids are observed. Single colonies are selected and their culture supernatants tested for binding activity against the polypeptide. Hybridomas having high reactivity and specificity are preferred.

Monoclonal antibodies may be isolated from the supernatants of growing hybridoma colonies. In addition, various techniques may be employed to enhance the yield, such as injection of the hybridoma cell line into the peritoneal cavity of a suitable vertebrate host, such as a mouse. Monoclonal antibodies may then be harvested from the ascites fluid or the blood. Contaminants may be removed from the antibodies by conventional techniques, such as chromatography, gel filtration, precipitation, and extraction. The polypeptides of this invention may be used in the purification process in, for example, an affinity chromatography step.

A number of therapeutically useful molecules are known in the art which comprise antigen-binding sites that are capable of exhibiting immunological binding properties of an antibody molecule. The proteolytic enzyme papain preferentially cleaves IgG molecules to yield several fragments, two of which (the "F(ab)" fragments) each comprise a covalent heterodimer that includes an intact antigen-binding site. The enzyme pepsin is able to cleave IgG molecules to provide several fragments, including the "F(ab')<sub>2</sub>" fragment which comprises both antigen-binding sites. An "Fv" fragment can be produced by preferential proteolytic cleavage of an IgM, and on rare occasions IgG or IgA immunoglobulin molecule. Fv fragments are, however, more commonly derived using recombinant techniques known in the art. The Fv fragment includes a non-covalent V<sub>H</sub>::V<sub>L</sub> heterodimer including an antigen-binding site which retains much of the antigen recognition and binding capabilities of the native antibody molecule. Inbar et al. (1972) Proc. Nat. Acad. Sci. USA 69:2659-2662; Hochman et al. (1976) Biochem 15:2706-2710; and Ehrlich et al. (1980) Biochem 19:4091-4096.

A single chain Fv ("sFv") polypeptide is a covalently linked V<sub>H</sub>::V<sub>L</sub> heterodimer which is expressed from a gene fusion including V<sub>H</sub>- and V<sub>L</sub>-encoding genes linked by a peptide-encoding linker. Huston et al. (1988) Proc. Nat. Acad. Sci. USA 85(16):5879-5883. A number of methods have been described to discern chemical structures for converting the naturally aggregated--but chemically separated--light and heavy polypeptide chains from an antibody V region into an sFv molecule which will fold into a three dimensional structure substantially similar to the structure of an

antigen-binding site. See, *e.g.*, U.S. Pat. Nos. 5,091,513 and 5,132,405, to Huston et al.; and U.S. Pat. No. 4,946,778, to Ladner et al.

Each of the above-described molecules includes a heavy chain and a light chain CDR set, respectively interposed between a heavy chain and a light chain FR set which provide support to the CDRS and define the spatial relationship of the CDRs relative to each other. As used herein, the term "CDR set" refers to the three hypervariable regions of a heavy or light chain V region. Proceeding from the N-terminus of a heavy or light chain, these regions are denoted as "CDR1," "CDR2," and "CDR3" respectively. An antigen-binding site, therefore, includes six CDRs, comprising the CDR set from each of a heavy and a light chain V region. A polypeptide comprising a single CDR, (*e.g.*, a CDR1, CDR2 or CDR3) is referred to herein as a "molecular recognition unit." Crystallographic analysis of a number of antigen-antibody complexes has demonstrated that the amino acid residues of CDRs form extensive contact with bound antigen, wherein the most extensive antigen contact is with the heavy chain CDR3. Thus, the molecular recognition units are primarily responsible for the specificity of an antigen-binding site.

As used herein, the term "FR set" refers to the four flanking amino acid sequences which frame the CDRs of a CDR set of a heavy or light chain V region. Some FR residues may contact bound antigen; however, FRs are primarily responsible for folding the V region into the antigen-binding site, particularly the FR residues directly adjacent to the CDRS. Within FRs, certain amino residues and certain structural features are very highly conserved. In this regard, all V region sequences contain an internal disulfide loop of around 90 amino acid residues. When the V regions fold into a binding-site, the CDRs are displayed as projecting loop motifs which form an antigen-binding surface. It is generally recognized that there are conserved structural regions of FRs which influence the folded shape of the CDR loops into certain "canonical" structures--regardless of the precise CDR amino acid sequence. Further, certain FR residues are known to participate in non-covalent interdomain contacts which stabilize the interaction of the antibody heavy and light chains.

A number of "humanized" antibody molecules comprising an antigen-binding site derived from a non-human immunoglobulin have been described, including chimeric antibodies having rodent V regions and their associated CDRs fused to human constant domains (Winter et al. (1991) *Nature* 349:293-299; Lobuglio et al. (1989) *Proc. Nat. Acad. Sci. USA* 86:4220-4224; Shaw et al. (1987) *J Immunol.* 138:4534-4538; and Brown et al. (1987) *Cancer Res.* 47:3577-3583), rodent CDRs grafted into a human supporting FR prior to fusion with an appropriate human antibody constant domain (Riechmann et al. (1988) *Nature* 332:323-327; Verhoeyen et al. (1988) *Science* 239:1534-1536; and Jones et al. (1986) *Nature* 321:522-525), and rodent CDRs supported by recombinantly veneered rodent FRs (European Patent Publication No. 519,596, published Dec. 23, 1992). These "humanized" molecules are designed to minimize unwanted immunological response toward rodent antihuman antibody molecules which limits the duration and effectiveness of therapeutic applications of those moieties in human recipients.

As used herein, the terms "veneered FRs" and "recombinantly veneered FRs" refer to the selective replacement of FR residues from, *e.g.*, a rodent heavy or light chain V region, with human FR residues in order to provide a xenogeneic molecule comprising an antigen-binding site which retains substantially all of the native FR polypeptide folding structure. Veneering techniques are based on the understanding that the ligand binding characteristics of an antigen-binding site are determined primarily by the structure and relative disposition of the heavy and light chain CDR sets within the antigen-binding surface. Davies et al. (1990) *Ann. Rev. Biochem.* 59:439-473. Thus, antigen binding specificity can be preserved in a humanized antibody only wherein the CDR structures, their interaction with each other, and their interaction with the rest of the V region domains are carefully maintained. By using veneering techniques, exterior (*e.g.*, solvent-accessible) FR residues which are readily encountered by the immune system are selectively replaced with human residues to provide a hybrid molecule that comprises either a weakly immunogenic, or substantially non-immunogenic veneered surface.

The process of veneering makes use of the available sequence data for human antibody variable domains compiled by Kabat et al., in Sequences of Proteins of Immunological Interest, 4th ed., (U.S. Dept. of Health and Human Services, U.S. Government Printing Office, 1987), updates to the Kabat database, and other accessible  
5 U.S. and foreign databases (both nucleic acid and protein). Solvent accessibilities of V region amino acids can be deduced from the known three-dimensional structure for human and murine antibody fragments. There are two general steps in veneering a murine antigen-binding site. Initially, the FRs of the variable domains of an antibody molecule of interest are compared with corresponding FR sequences of human variable  
10 domains obtained from the above-identified sources. The most homologous human V regions are then compared residue by residue to corresponding murine amino acids. The residues in the murine FR which differ from the human counterpart are replaced by the residues present in the human moiety using recombinant techniques well known in the art. Residue switching is only carried out with moieties which are at least partially  
15 exposed (solvent accessible), and care is exercised in the replacement of amino acid residues which may have a significant effect on the tertiary structure of V region domains, such as proline, glycine and charged amino acids.

In this manner, the resultant "veneered" murine antigen-binding sites are thus designed to retain the murine CDR residues, the residues substantially adjacent to  
20 the CDRs, the residues identified as buried or mostly buried (solvent inaccessible), the residues believed to participate in non-covalent (*e.g.*, electrostatic and hydrophobic) contacts between heavy and light chain domains, and the residues from conserved structural regions of the FRs which are believed to influence the "canonical" tertiary structures of the CDR loops. These design criteria are then used to prepare recombinant  
25 nucleotide sequences which combine the CDRs of both the heavy and light chain of a murine antigen-binding site into human-appearing FRs that can be used to transfect mammalian cells for the expression of recombinant human antibodies which exhibit the antigen specificity of the murine antibody molecule.

In another embodiment of the invention, monoclonal antibodies of the  
30 present invention may be coupled to one or more therapeutic agents. Suitable agents in

this regard include radionuclides, differentiation inducers, drugs, toxins, and derivatives thereof. Preferred radionuclides include  $^{90}\text{Y}$ ,  $^{123}\text{I}$ ,  $^{125}\text{I}$ ,  $^{131}\text{I}$ ,  $^{186}\text{Re}$ ,  $^{188}\text{Re}$ ,  $^{211}\text{At}$ , and  $^{212}\text{Bi}$ . Preferred drugs include methotrexate, and pyrimidine and purine analogs. Preferred differentiation inducers include phorbol esters and butyric acid. Preferred  
5 toxins include ricin, abrin, diphtheria toxin, cholera toxin, gelonin, *Pseudomonas* exotoxin, Shigella toxin, and pokeweed antiviral protein.

A therapeutic agent may be coupled (*e.g.*, covalently bonded) to a suitable monoclonal antibody either directly or indirectly (*e.g.*, via a linker group). A direct reaction between an agent and an antibody is possible when each possesses a  
10 substituent capable of reacting with the other. For example, a nucleophilic group, such as an amino or sulfhydryl group, on one may be capable of reacting with a carbonyl-containing group, such as an anhydride or an acid halide, or with an alkyl group containing a good leaving group (*e.g.*, a halide) on the other.

Alternatively, it may be desirable to couple a therapeutic agent and an  
15 antibody via a linker group. A linker group can function as a spacer to distance an antibody from an agent in order to avoid interference with binding capabilities. A linker group can also serve to increase the chemical reactivity of a substituent on an agent or an antibody, and thus increase the coupling efficiency. An increase in chemical reactivity may also facilitate the use of agents, or functional groups on agents, which  
20 otherwise would not be possible.

It will be evident to those skilled in the art that a variety of bifunctional or polyfunctional reagents, both homo- and hetero-functional (such as those described in the catalog of the Pierce Chemical Co., Rockford, IL), may be employed as the linker group. Coupling may be effected, for example, through amino groups, carboxyl groups,  
25 sulfhydryl groups or oxidized carbohydrate residues. There are numerous references describing such methodology, *e.g.*, U.S. Patent No. 4,671,958, to Rodwell et al.

Where a therapeutic agent is more potent when free from the antibody portion of the immunoconjugates of the present invention, it may be desirable to use a linker group which is cleavable during or upon internalization into a cell. A number of  
30 different cleavable linker groups have been described. The mechanisms for the



intracellular release of an agent from these linker groups include cleavage by reduction of a disulfide bond (*e.g.*, U.S. Patent No. 4,489,710, to Spitler), by irradiation of a photolabile bond (*e.g.*, U.S. Patent No. 4,625,014, to Senter et al.), by hydrolysis of derivatized amino acid side chains (*e.g.*, U.S. Patent No. 4,638,045, to Kohn et al.), by  
5 serum complement-mediated hydrolysis (*e.g.*, U.S. Patent No. 4,671,958, to Rodwell et al.), and acid-catalyzed hydrolysis (*e.g.*, U.S. Patent No. 4,569,789, to Blattler et al.).

It may be desirable to couple more than one agent to an antibody. In one embodiment, multiple molecules of an agent are coupled to one antibody molecule. In another embodiment, more than one type of agent may be coupled to one antibody.  
10 Regardless of the particular embodiment, immunoconjugates with more than one agent may be prepared in a variety of ways. For example, more than one agent may be coupled directly to an antibody molecule, or linkers that provide multiple sites for attachment can be used. Alternatively, a carrier can be used.

A carrier may bear the agents in a variety of ways, including covalent  
15 bonding either directly or via a linker group. Suitable carriers include proteins such as albumins (*e.g.*, U.S. Patent No. 4,507,234, to Kato et al.), peptides and polysaccharides such as aminodextran (*e.g.*, U.S. Patent No. 4,699,784, to Shih et al.). A carrier may also bear an agent by noncovalent bonding or by encapsulation, such as within a liposome vesicle (*e.g.*, U.S. Patent Nos. 4,429,008 and 4,873,088). Carriers specific for  
20 radionuclide agents include radiohalogenated small molecules and chelating compounds. For example, U.S. Patent No. 4,735,792 discloses representative radiohalogenated small molecules and their synthesis. A radionuclide chelate may be formed from chelating compounds that include those containing nitrogen and sulfur atoms as the donor atoms for binding the metal, or metal oxide, radionuclide. For  
25 example, U.S. Patent No. 4,673,562, to Davison et al. discloses representative chelating compounds and their synthesis.

### T Cell Compositions

The present invention, in another aspect, provides T cells specific for a tumor polypeptide disclosed herein, or for a variant or derivative thereof. Such cells

may generally be prepared *in vitro* or *ex vivo*, using standard procedures. For example, T cells may be isolated from bone marrow, peripheral blood, or a fraction of bone marrow or peripheral blood of a patient, using a commercially available cell separation system, such as the Isolex™ System, available from Nexell Therapeutics, Inc. (Irvine, CA; see also U.S. Patent No. 5,240,856; U.S. Patent No. 5,215,926; WO 89/06280; WO 91/16116 and WO 92/07243). Alternatively, T cells may be derived from related or unrelated humans, non-human mammals, cell lines or cultures.

T cells may be stimulated with a polypeptide, polynucleotide encoding a polypeptide and/or an antigen presenting cell (APC) that expresses such a polypeptide. Such stimulation is performed under conditions and for a time sufficient to permit the generation of T cells that are specific for the polypeptide of interest. Preferably, a tumor polypeptide or polynucleotide of the invention is present within a delivery vehicle, such as a microsphere, to facilitate the generation of specific T cells.

T cells are considered to be specific for a polypeptide of the present invention if the T cells specifically proliferate, secrete cytokines or kill target cells coated with the polypeptide or expressing a gene encoding the polypeptide. T cell specificity may be evaluated using any of a variety of standard techniques. For example, within a chromium release assay or proliferation assay, a stimulation index of more than two fold increase in lysis and/or proliferation, compared to negative controls, indicates T cell specificity. Such assays may be performed, for example, as described in Chen et al., *Cancer Res.* 54:1065-1070, 1994. Alternatively, detection of the proliferation of T cells may be accomplished by a variety of known techniques. For example, T cell proliferation can be detected by measuring an increased rate of DNA synthesis (*e.g.*, by pulse-labeling cultures of T cells with tritiated thymidine and measuring the amount of tritiated thymidine incorporated into DNA). Contact with a tumor polypeptide (100 ng/ml - 100 µg/ml, preferably 200 ng/ml - 25 µg/ml) for 3 - 7 days will typically result in at least a two fold increase in proliferation of the T cells. Contact as described above for 2-3 hours should result in activation of the T cells, as measured using standard cytokine assays in which a two fold increase in the level of cytokine release (*e.g.*, TNF or IFN-γ) is indicative of T cell activation (*see* Coligan et

al., Current Protocols in Immunology, vol. 1, Wiley Interscience (Greene 1998)). T cells that have been activated in response to a tumor polypeptide, polynucleotide or polypeptide-expressing APC may be CD4<sup>+</sup> and/or CD8<sup>+</sup>. Tumor polypeptide-specific T cells may be expanded using standard techniques. Within preferred embodiments, the T  
5 cells are derived from a patient, a related donor or an unrelated donor, and are administered to the patient following stimulation and expansion.

For therapeutic purposes, CD4<sup>+</sup> or CD8<sup>+</sup> T cells that proliferate in response to a tumor polypeptide, polynucleotide or APC can be expanded in number either *in vitro* or *in vivo*. Proliferation of such T cells *in vitro* may be accomplished in a  
10 variety of ways. For example, the T cells can be re-exposed to a tumor polypeptide, or a short peptide corresponding to an immunogenic portion of such a polypeptide, with or without the addition of T cell growth factors, such as interleukin-2, and/or stimulator cells that synthesize a tumor polypeptide. Alternatively, one or more T cells that proliferate in the presence of the tumor polypeptide can be expanded in number by  
15 cloning. Methods for cloning cells are well known in the art, and include limiting dilution.

#### Pharmaceutical Compositions

In additional embodiments, the present invention concerns formulation of one or more of the polynucleotide, polypeptide, T-cell and/or antibody compositions  
20 disclosed herein in pharmaceutically-acceptable carriers for administration to a cell or an animal, either alone, or in combination with one or more other modalities of therapy.

It will be understood that, if desired, a composition as disclosed herein may be administered in combination with other agents as well, such as, *e.g.*, other proteins or polypeptides or various pharmaceutically-active agents. In fact, there is  
25 virtually no limit to other components that may also be included, given that the additional agents do not cause a significant adverse effect upon contact with the target cells or host tissues. The compositions may thus be delivered along with various other agents as required in the particular instance. Such compositions may be purified from host cells or other biological sources, or alternatively may be chemically synthesized as

described herein. Likewise, such compositions may further comprise substituted or derivatized RNA or DNA compositions.

Therefore, in another aspect of the present invention, pharmaceutical compositions are provided comprising one or more of the polynucleotide, polypeptide, antibody, and/or T-cell compositions described herein in combination with a physiologically acceptable carrier. In certain preferred embodiments, the pharmaceutical compositions of the invention comprise immunogenic polynucleotide and/or polypeptide compositions of the invention for use in prophylactic and therapeutic vaccine applications. Vaccine preparation is generally described in, for example, M.F. Powell and M.J. Newman, eds., "Vaccine Design (the subunit and adjuvant approach)," Plenum Press (NY, 1995). Generally, such compositions will comprise one or more polynucleotide and/or polypeptide compositions of the present invention in combination with one or more immunostimulants.

It will be apparent that any of the pharmaceutical compositions described herein can contain pharmaceutically acceptable salts of the polynucleotides and polypeptides of the invention. Such salts can be prepared, for example, from pharmaceutically acceptable non-toxic bases, including organic bases (e.g., salts of primary, secondary and tertiary amines and basic amino acids) and inorganic bases (e.g., sodium, potassium, lithium, ammonium, calcium and magnesium salts).

In another embodiment, illustrative immunogenic compositions, e.g., vaccine compositions, of the present invention comprise DNA encoding one or more of the polypeptides as described above, such that the polypeptide is generated *in situ*. As noted above, the polynucleotide may be administered within any of a variety of delivery systems known to those of ordinary skill in the art. Indeed, numerous gene delivery techniques are well known in the art, such as those described by Rolland, *Crit. Rev. Therap. Drug Carrier Systems* 15:143-198, 1998, and references cited therein. Appropriate polynucleotide expression systems will, of course, contain the necessary regulatory DNA regulatory sequences for expression in a patient (such as a suitable promoter and terminating signal). Alternatively, bacterial delivery systems may involve

the administration of a bacterium (such as *Bacillus-Calmette-Guerrin*) that expresses an immunogenic portion of the polypeptide on its cell surface or secretes such an epitope.

Therefore, in certain embodiments, polynucleotides encoding immunogenic polypeptides described herein are introduced into suitable mammalian host cells for expression using any of a number of known viral-based systems. In one illustrative embodiment, retroviruses provide a convenient and effective platform for gene delivery systems. A selected nucleotide sequence encoding a polypeptide of the present invention can be inserted into a vector and packaged in retroviral particles using techniques known in the art. The recombinant virus can then be isolated and delivered to a subject. A number of illustrative retroviral systems have been described (*e.g.*, U.S. Pat. No. 5,219,740; Miller and Rosman (1989) *BioTechniques* 7:980-990; Miller, A. D. (1990) *Human Gene Therapy* 1:5-14; Scarpa et al. (1991) *Virology* 180:849-852; Burns et al. (1993) *Proc. Natl. Acad. Sci. USA* 90:8033-8037; and Boris-Lawrie and Temin (1993) *Cur. Opin. Genet. Develop.* 3:102-109.

In addition, a number of illustrative adenovirus-based systems have also been described. Unlike retroviruses which integrate into the host genome, adenoviruses persist extrachromosomally thus minimizing the risks associated with insertional mutagenesis (Haj-Ahmad and Graham (1986) *J. Virol.* 57:267-274; Bett et al. (1993) *J. Virol.* 67:5911-5921; Mittereder et al. (1994) *Human Gene Therapy* 5:717-729; Seth et al. (1994) *J. Virol.* 68:933-940; Barr et al. (1994) *Gene Therapy* 1:51-58; Berkner, K. L. (1988) *BioTechniques* 6:616-629; and Rich et al. (1993) *Human Gene Therapy* 4:461-476).

Various adeno-associated virus (AAV) vector systems have also been developed for polynucleotide delivery. AAV vectors can be readily constructed using techniques well known in the art. See, *e.g.*, U.S. Pat. Nos. 5,173,414 and 5,139,941; International Publication Nos. WO 92/01070 and WO 93/03769; Lebkowski et al. (1988) *Molec. Cell. Biol.* 8:3988-3996; Vincent et al. (1990) *Vaccines* 90 (Cold Spring Harbor Laboratory Press); Carter, B. J. (1992) *Current Opinion in Biotechnology* 3:533-539; Muzyczka, N. (1992) *Current Topics in Microbiol. and Immunol.* 158:97-129;

Kotin, R. M. (1994) Human Gene Therapy 5:793-801; Shelling and Smith (1994) Gene Therapy 1:165-169; and Zhou et al. (1994) J. Exp. Med. 179:1867-1875.

Additional viral vectors useful for delivering the polynucleotides encoding polypeptides of the present invention by gene transfer include those derived from the pox family of viruses, such as vaccinia virus and avian poxvirus. By way of example, vaccinia virus recombinants expressing the novel molecules can be constructed as follows. The DNA encoding a polypeptide is first inserted into an appropriate vector so that it is adjacent to a vaccinia promoter and flanking vaccinia DNA sequences, such as the sequence encoding thymidine kinase (TK). This vector is then used to transfect cells which are simultaneously infected with vaccinia. Homologous recombination serves to insert the vaccinia promoter plus the gene encoding the polypeptide of interest into the viral genome. The resulting TK.sup.(-) recombinant can be selected by culturing the cells in the presence of 5-bromodeoxyuridine and picking viral plaques resistant thereto.

A vaccinia-based infection/transfection system can be conveniently used to provide for inducible, transient expression or coexpression of one or more polypeptides described herein in host cells of an organism. In this particular system, cells are first infected in vitro with a vaccinia virus recombinant that encodes the bacteriophage T7 RNA polymerase. This polymerase displays exquisite specificity in that it only transcribes templates bearing T7 promoters. Following infection, cells are transfected with the polynucleotide or polynucleotides of interest, driven by a T7 promoter. The polymerase expressed in the cytoplasm from the vaccinia virus recombinant transcribes the transfected DNA into RNA which is then translated into polypeptide by the host translational machinery. The method provides for high level, transient, cytoplasmic production of large quantities of RNA and its translation products. See, e.g., Elroy-Stein and Moss, Proc. Natl. Acad. Sci. USA (1990) 87:6743-6747; Fuerst et al. Proc. Natl. Acad. Sci. USA (1986) 83:8122-8126.

Alternatively, avipoxviruses, such as the fowlpox and canarypox viruses, can also be used to deliver the coding sequences of interest. Recombinant avipox viruses, expressing immunogens from mammalian pathogens, are known to confer

protective immunity when administered to non-avian species. The use of an Avipox vector is particularly desirable in human and other mammalian species since members of the Avipox genus can only productively replicate in susceptible avian species and therefore are not infective in mammalian cells. Methods for producing recombinant  
5 Avipoxviruses are known in the art and employ genetic recombination, as described above with respect to the production of vaccinia viruses. See, *e.g.*, WO 91/12882; WO 89/03429; and WO 92/03545.

Any of a number of alphavirus vectors can also be used for delivery of polynucleotide compositions of the present invention, such as those vectors described in  
10 U.S. Patent Nos. 5,843,723; 6,015,686; 6,008,035 and 6,015,694. Certain vectors based on Venezuelan Equine Encephalitis (VEE) can also be used, illustrative examples of which can be found in U.S. Patent Nos. 5,505,947 and 5,643,576.

Moreover, molecular conjugate vectors, such as the adenovirus chimeric vectors described in Michael et al. *J. Biol. Chem.* (1993) 268:6866-6869 and Wagner et  
15 al. *Proc. Natl. Acad. Sci. USA* (1992) 89:6099-6103, can also be used for gene delivery under the invention.

Additional illustrative information on these and other known viral-based delivery systems can be found, for example, in Fisher-Hoch et al., *Proc. Natl. Acad. Sci. USA* 86:317-321, 1989; Flexner et al., *Ann. N.Y. Acad. Sci.* 569:86-103, 1989; Flexner  
20 et al., *Vaccine* 8:17-21, 1990; U.S. Patent Nos. 4,603,112, 4,769,330, and 5,017,487; WO 89/01973; U.S. Patent No. 4,777,127; GB 2,200,651; EP 0,345,242; WO 91/02805; Berkner, *Biotechniques* 6:616-627, 1988; Rosenfeld et al., *Science* 252:431-434, 1991; Kolls et al., *Proc. Natl. Acad. Sci. USA* 91:215-219, 1994; Kass-Eisler et al., *Proc. Natl. Acad. Sci. USA* 90:11498-11502, 1993; Guzman et al.,  
25 *Circulation* 88:2838-2848, 1993; and Guzman et al., *Cir. Res.* 73:1202-1207, 1993.

In certain embodiments, a polynucleotide may be integrated into the genome of a target cell. This integration may be in a specific location and orientation *via* homologous recombination (gene replacement) or it may be integrated in a random, non-specific location (gene augmentation). In yet further embodiments, the  
30 polynucleotide may be stably maintained in the cell as a separate, episomal segment of

DNA. Such polynucleotide segments or "episomes" encode sequences sufficient to permit maintenance and replication independent of or in synchronization with the host cell cycle. **The manner in which the expression construct is delivered to a cell and where in the cell the polynucleotide remains is dependent on the type of expression**  
5 construct employed.

In another embodiment of the invention, a polynucleotide is administered/delivered as "naked" DNA, for example as described in Ulmer et al., *Science* 259:1745-1749, 1993 and reviewed by Cohen, *Science* 259:1691-1692, 1993. The uptake of naked DNA may be increased by coating the DNA onto biodegradable  
10 beads, which are efficiently transported into the cells.

In still another embodiment, a composition of the present invention can be delivered via a particle bombardment approach, many of which have been described. In one illustrative example, gas-driven particle acceleration can be achieved with devices such as those manufactured by Powderject Pharmaceuticals PLC (Oxford, UK)  
15 and Powderject Vaccines Inc. (Madison, WI), some examples of which are described in U.S. Patent Nos. 5,846,796; 6,010,478; 5,865,796; 5,584,807; and EP Patent No. 0500 799. This approach offers a needle-free delivery approach wherein a dry powder formulation of microscopic particles, such as polynucleotide or polypeptide particles, are accelerated to high speed within a helium gas jet generated by a hand held device,  
20 propelling the particles into a target tissue of interest.

In a related embodiment, other devices and methods that may be useful for gas-driven needle-less injection of compositions of the present invention include those provided by Bioject, Inc. (Portland, OR), some examples of which are described in U.S. Patent Nos. 4,790,824; 5,064,413; 5,312,335; 5,383,851; 5,399,163; 5,520,639  
25 and 5,993,412.

According to another embodiment, the pharmaceutical compositions described herein will comprise one or more immunostimulants in addition to the immunogenic polynucleotide, polypeptide, antibody, T-cell and/or APC compositions of this invention. An immunostimulant refers to essentially any substance that enhances  
30 or potentiates an immune response (antibody and/or cell-mediated) to an exogenous



antigen. One preferred type of immunostimulant comprises an adjuvant. Many adjuvants contain a substance designed to protect the antigen from rapid catabolism, such as aluminum hydroxide or mineral oil, and a stimulator of immune responses, such as lipid A, *Bordetella pertussis* or *Mycobacterium tuberculosis* derived proteins.

5 Certain adjuvants are commercially available as, for example, Freund's Incomplete Adjuvant and Complete Adjuvant (Difco Laboratories, Detroit, MI); Merck Adjuvant 65 (Merck and Company, Inc., Rahway, NJ); AS-2 (SmithKline Beecham, Philadelphia, PA); aluminum salts such as aluminum hydroxide gel (alum) or aluminum phosphate; salts of calcium, iron or zinc; an insoluble suspension of acylated tyrosine; acylated  
10 sugars; cationically or anionically derivatized polysaccharides; polyphosphazenes; biodegradable microspheres; monophosphoryl lipid A and quil A. Cytokines, such as GM-CSF, interleukin-2, -7, -12, and other like growth factors, may also be used as adjuvants.

Within certain embodiments of the invention, the adjuvant composition  
15 is preferably one that induces an immune response predominantly of the Th1 type. High levels of Th1-type cytokines (e.g., IFN- $\gamma$ , TNF $\alpha$ , IL-2 and IL-12) tend to favor the induction of cell mediated immune responses to an administered antigen. In contrast, high levels of Th2-type cytokines (e.g., IL-4, IL-5, IL-6 and IL-10) tend to favor the induction of humoral immune responses. Following application of a vaccine as  
20 provided herein, a patient will support an immune response that includes Th1- and Th2-type responses. Within a preferred embodiment, in which a response is predominantly Th1-type, the level of Th1-type cytokines will increase to a greater extent than the level of Th2-type cytokines. The levels of these cytokines may be readily assessed using standard assays. For a review of the families of cytokines, see Mosmann and Coffman,  
25 *Ann. Rev. Immunol.* 7:145-173, 1989.

Certain preferred adjuvants for eliciting a predominantly Th1-type response include, for example, a combination of monophosphoryl lipid A, preferably 3-de-O-acylated monophosphoryl lipid A, together with an aluminum salt. MPL<sup>®</sup> adjuvants are available from Corixa Corporation (Seattle, WA; see, for example, US  
30 Patent Nos. 4,436,727; 4,877,611; 4,866,034 and 4,912,094). CpG-containing

oligonucleotides (in which the CpG dinucleotide is unmethylated) also induce a predominantly Th1 response. Such oligonucleotides are well known and are described, for example, in WO 96/02555, WO 99/33488 and U.S. Patent Nos. 6,008,200 and 5,856,462. Immunostimulatory DNA sequences are also described, for example, by  
5 Sato et al., *Science* 273:352, 1996. Another preferred adjuvant comprises a saponin, such as Quil A, or derivatives thereof, including QS21 and QS7 (Aquila Biopharmaceuticals Inc., Framingham, MA); Escin; Digitonin; or *Gypsophila* or *Chenopodium quinoa* saponins. Other preferred formulations include more than one saponin in the adjuvant combinations of the present invention, for example  
10 combinations of at least two of the following group comprising QS21, QS7, Quil A,  $\beta$ -escin, or digitonin.

Alternatively the saponin formulations may be combined with vaccine vehicles composed of chitosan or other polycationic polymers, polylactide and polylactide-co-glycolide particles, poly-N-acetyl glucosamine-based polymer matrix,  
15 particles composed of polysaccharides or chemically modified polysaccharides, liposomes and lipid-based particles, particles composed of glycerol monoesters, etc. The saponins may also be formulated in the presence of cholesterol to form particulate structures such as liposomes or ISCOMs. Furthermore, the saponins may be formulated together with a polyoxyethylene ether or ester, in either a non-particulate solution or  
20 suspension, or in a particulate structure such as a paucilamellar liposome or ISCOM. The saponins may also be formulated with excipients such as Carbopol<sup>R</sup> to increase viscosity, or may be formulated in a dry powder form with a powder excipient such as lactose.

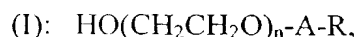
In one preferred embodiment, the adjuvant system includes the  
25 combination of a monophosphoryl lipid A and a saponin derivative, such as the combination of QS21 and 3D-MPL<sup>®</sup> adjuvant, as described in WO 94/00153, or a less reactogenic composition where the QS21 is quenched with cholesterol, as described in WO 96/33739. Other preferred formulations comprise an oil-in-water emulsion and tocopherol. Another particularly preferred adjuvant formulation employing QS21, 3D-

MPL<sup>®</sup> adjuvant and tocopherol in an oil-in-water emulsion is described in WO 95/17210.

Another enhanced adjuvant system involves the combination of a CpG-containing oligonucleotide and a saponin derivative particularly the combination of  
5 CpG and QS21 is disclosed in WO 00/09159. Preferably the formulation additionally comprises an oil in water emulsion and tocopherol.

Additional illustrative adjuvants for use in the pharmaceutical compositions of the invention include Montanide ISA 720 (Seppic, France), SAF (Chiron, California, United States), ISCOMS (CSL), MF-59 (Chiron), the SBAS series  
10 of adjuvants (e.g., SBAS-2 or SBAS-4, available from SmithKline Beecham, Rixensart, Belgium), Detox (Enhanzyn<sup>®</sup>; Corixa, Hamilton, MT), RC-529 (Corixa, Hamilton, MT) and other aminoalkyl glucosaminide 4-phosphates (AGPs), such as those described in pending U.S. Patent Application Serial Nos. 08/853,826 and 09/074,720, the disclosures of which are incorporated herein by reference in their entireties, and polyoxyethylene  
15 ether adjuvants such as those described in WO 99/52549A1.

Other preferred adjuvants include adjuvant molecules of the general formula



wherein,  $n$  is 1-50,  $A$  is a bond or  $-\text{C}(\text{O})-$ ,  $R$  is  $\text{C}_{1-50}$  alkyl or Phenyl  $\text{C}_{1-50}$  alkyl.

20 One embodiment of the present invention consists of a vaccine formulation comprising a polyoxyethylene ether of general formula (I), wherein  $n$  is between 1 and 50, preferably 4-24, most preferably 9; the  $R$  component is  $\text{C}_{1-50}$ , preferably  $\text{C}_4\text{-C}_{20}$  alkyl and most preferably  $\text{C}_{12}$  alkyl, and  $A$  is a bond. The concentration of the polyoxyethylene ethers should be in the range 0.1-20%, preferably  
25 from 0.1-10%, and most preferably in the range 0.1-1%. Preferred polyoxyethylene ethers are selected from the following group: polyoxyethylene-9-lauryl ether, polyoxyethylene-9-stearyl ether, polyoxyethylene-8-stearyl ether, polyoxyethylene-4-lauryl ether, polyoxyethylene-35-lauryl ether, and polyoxyethylene-23-lauryl ether. Polyoxyethylene ethers such as polyoxyethylene lauryl ether are described in the Merck  
30 index (12<sup>th</sup> edition: entry 7717). These adjuvant molecules are described in WO

99/52549. The polyoxyethylene ether according to the general formula (I) above may, if desired, be combined with another adjuvant. For example, a preferred adjuvant combination is preferably with CpG as described in the pending UK patent application GB 9820956.2.

5                   According to another embodiment of this invention, an immunogenic composition described herein is delivered to a host via antigen presenting cells (APCs), such as dendritic cells, macrophages, B cells, monocytes and other cells that may be engineered to be efficient APCs. Such cells may, but need not, be genetically modified to increase the capacity for presenting the antigen, to improve activation and/or  
10 maintenance of the T cell response, to have anti-tumor effects *per se* and/or to be immunologically compatible with the receiver (*i.e.*, matched HLA haplotype). APCs may generally be isolated from any of a variety of biological fluids and organs, including tumor and peritumoral tissues, and may be autologous, allogeneic, syngeneic or xenogeneic cells.

15                   Certain preferred embodiments of the present invention use dendritic cells or progenitors thereof as antigen-presenting cells. Dendritic cells are highly potent APCs (Banchereau and Steinman, *Nature* 392:245-251, 1998) and have been shown to be effective as a physiological adjuvant for eliciting prophylactic or therapeutic antitumor immunity (*see* Timmerman and Levy, *Ann. Rev. Med.* 50:507-529, 1999). In  
20 general, dendritic cells may be identified based on their typical shape (stellate *in situ*, with marked cytoplasmic processes (dendrites) visible *in vitro*), their ability to take up, process and present antigens with high efficiency and their ability to activate naïve T cell responses. Dendritic cells may, of course, be engineered to express specific cell-surface receptors or ligands that are not commonly found on dendritic cells *in vivo* or *ex*  
25 *vivo*, and such modified dendritic cells are contemplated by the present invention. As an alternative to dendritic cells, secreted vesicles antigen-loaded dendritic cells (called exosomes) may be used within a vaccine (*see* Zitvogel et al., *Nature Med.* 4:594-600, 1998).

                  Dendritic cells and progenitors may be obtained from peripheral blood,  
30 bone marrow, tumor-infiltrating cells, peritumoral tissues-infiltrating cells, lymph

nodes, spleen, skin, umbilical cord blood or any other suitable tissue or fluid. For example, dendritic cells may be differentiated *ex vivo* by adding a combination of cytokines such as GM-CSF, IL-4, IL-13 and/or TNF $\alpha$  to cultures of monocytes harvested from peripheral blood. Alternatively, CD34 positive cells harvested from  
5 peripheral blood, umbilical cord blood or bone marrow may be differentiated into dendritic cells by adding to the culture medium combinations of GM-CSF, IL-3, TNF $\alpha$ , CD40 ligand, LPS, flt3 ligand and/or other compound(s) that induce differentiation, maturation and proliferation of dendritic cells.

Dendritic cells are conveniently categorized as "immature" and "mature"  
10 cells, which allows a simple way to discriminate between two well characterized phenotypes. However, this nomenclature should not be construed to exclude all possible intermediate stages of differentiation. Immature dendritic cells are characterized as APC with a high capacity for antigen uptake and processing, which correlates with the high expression of Fc $\gamma$  receptor and mannose receptor. The mature  
15 phenotype is typically characterized by a lower expression of these markers, but a high expression of cell surface molecules responsible for T cell activation such as class I and class II MHC, adhesion molecules (*e.g.*, CD54 and CD11) and costimulatory molecules (*e.g.*, CD40, CD80, CD86 and 4-1BB).

APCs may generally be transfected with a polynucleotide of the  
20 invention (or portion or other variant thereof) such that the encoded polypeptide, or an immunogenic portion thereof, is expressed on the cell surface. Such transfection may take place *ex vivo*, and a pharmaceutical composition comprising such transfected cells may then be used for therapeutic purposes, as described herein. Alternatively, a gene delivery vehicle that targets a dendritic or other antigen presenting cell may be  
25 administered to a patient, resulting in transfection that occurs *in vivo*. *In vivo* and *ex vivo* transfection of dendritic cells, for example, may generally be performed using any methods known in the art, such as those described in WO 97/24447, or the gene gun approach described by Mahvi et al., *Immunology and cell Biology* 75:456-460, 1997. Antigen loading of dendritic cells may be achieved by incubating dendritic cells or  
30 progenitor cells with the tumor polypeptide, DNA (naked or within a plasmid vector) or

RNA; or with antigen-expressing recombinant bacterium or viruses (*e.g.*, vaccinia, fowlpox, adenovirus or lentivirus vectors). Prior to loading, the polypeptide may be covalently conjugated to an immunological partner that provides T cell help (*e.g.*, a carrier molecule). Alternatively, a dendritic cell may be pulsed with a non-conjugated  
5 immunological partner, separately or in the presence of the polypeptide.

While any suitable carrier known to those of ordinary skill in the art may be employed in the pharmaceutical compositions of this invention, the type of carrier will typically vary depending on the mode of administration. Compositions of the present invention may be formulated for any appropriate manner of administration,  
10 including for example, topical, oral, nasal, mucosal, intravenous, intracranial, intraperitoneal, subcutaneous and intramuscular administration.

Carriers for use within such pharmaceutical compositions are biocompatible, and may also be biodegradable. In certain embodiments, the formulation preferably provides a relatively constant level of active component release.  
15 In other embodiments, however, a more rapid rate of release immediately upon administration may be desired. The formulation of such compositions is well within the level of ordinary skill in the art using known techniques. Illustrative carriers useful in this regard include microparticles of poly(lactide-co-glycolide), polyacrylate, latex, starch, cellulose, dextran and the like. Other illustrative delayed-release carriers  
20 include supramolecular biovectors, which comprise a non-liquid hydrophilic core (*e.g.*, a cross-linked polysaccharide or oligosaccharide) and, optionally, an external layer comprising an amphiphilic compound, such as a phospholipid (*see e.g.*, U.S. Patent No. 5,151,254 and PCT applications WO 94/20078, WO/94/23701 and WO 96/06638). The amount of active compound contained within a sustained release formulation depends  
25 upon the site of implantation, the rate and expected duration of release and the nature of the condition to be treated or prevented.

In another illustrative embodiment, biodegradable microspheres (*e.g.*, polylactate polyglycolate) are employed as carriers for the compositions of this invention. Suitable biodegradable microspheres are disclosed, for example, in U.S.  
30 Patent Nos. 4,897,268; 5,075,109; 5,928,647; 5,811,128; 5,820,883; 5,853,763;

5.814,344, 5.407,609 and 5,942,252. Modified hepatitis B core protein carrier systems, such as described in WO/99 40934, and references cited therein, will also be useful for many applications. Another illustrative carrier/delivery system employs a carrier comprising particulate-protein complexes, such as those described in U.S. Patent No.  
5 5,928,647, which are capable of inducing a class I-restricted cytotoxic T lymphocyte responses in a host.

The pharmaceutical compositions of the invention will often further comprise one or more buffers (*e.g.*, neutral buffered saline or phosphate buffered saline), carbohydrates (*e.g.*, glucose, mannose, sucrose or dextrans), mannitol, proteins,  
10 polypeptides or amino acids such as glycine, antioxidants, bacteriostats, chelating agents such as EDTA or glutathione, adjuvants (*e.g.*, aluminum hydroxide), solutes that render the formulation isotonic, hypotonic or weakly hypertonic with the blood of a recipient, suspending agents, thickening agents and/or preservatives. Alternatively, compositions of the present invention may be formulated as a lyophilizate.

15 The pharmaceutical compositions described herein may be presented in unit-dose or multi-dose containers, such as sealed ampoules or vials. Such containers are typically sealed in such a way to preserve the sterility and stability of the formulation until use. In general, formulations may be stored as suspensions, solutions or emulsions in oily or aqueous vehicles. Alternatively, a pharmaceutical composition  
20 may be stored in a freeze-dried condition requiring only the addition of a sterile liquid carrier immediately prior to use.

The development of suitable dosing and treatment regimens for using the particular compositions described herein in a variety of treatment regimens, including *e.g.*, oral, parenteral, intravenous, intranasal, and intramuscular administration and  
25 formulation, is well known in the art, some of which are briefly discussed below for general purposes of illustration.

In certain applications, the pharmaceutical compositions disclosed herein may be delivered *via* oral administration to an animal. As such, these compositions may be formulated with an inert diluent or with an assimilable edible carrier, or they

may be enclosed in hard- or soft-shell gelatin capsule, or they may be compressed into tablets, or they may be incorporated directly with the food of the diet.

The active compounds may even be incorporated with excipients and used in the form of ingestible tablets, buccal tables, troches, capsules, elixirs, suspensions, syrups, wafers, and the like (see, for example, Mathiowitz *et al.*, Nature 1997 Mar 27;386(6623):410-4; Hwang *et al.*, Crit Rev Ther Drug Carrier Syst 1998;15(3):243-84; U. S. Patent 5,641,515; U. S. Patent 5,580,579 and U. S. Patent 5,792,451). Tablets, troches, pills, capsules and the like may also contain any of a variety of additional components, for example, a binder, such as gum tragacanth, acacia, cornstarch, or gelatin; excipients, such as dicalcium phosphate; a disintegrating agent, such as corn starch, potato starch, alginic acid and the like; a lubricant, such as magnesium stearate; and a sweetening agent, such as sucrose, lactose or saccharin may be added or a flavoring agent, such as peppermint, oil of wintergreen, or cherry flavoring. When the dosage unit form is a capsule, it may contain, in addition to materials of the above type, a liquid carrier. Various other materials may be present as coatings or to otherwise modify the physical form of the dosage unit. For instance, tablets, pills, or capsules may be coated with shellac, sugar, or both. Of course, any material used in preparing any dosage unit form should be pharmaceutically pure and substantially non-toxic in the amounts employed. In addition, the active compounds may be incorporated into sustained-release preparation and formulations.

Typically, these formulations will contain at least about 0.1% of the active compound or more, although the percentage of the active ingredient(s) may, of course, be varied and may conveniently be between about 1 or 2% and about 60% or 70% or more of the weight or volume of the total formulation. Naturally, the amount of active compound(s) in each therapeutically useful composition may be prepared in such a way that a suitable dosage will be obtained in any given unit dose of the compound. Factors such as solubility, bioavailability, biological half-life, route of administration, product shelf life, as well as other pharmacological considerations will be contemplated by one skilled in the art of preparing such pharmaceutical formulations, and as such, a variety of dosages and treatment regimens may be desirable.



For oral administration, the compositions of the present invention may alternatively be incorporated with one or more excipients in the form of a mouthwash, dentifrice, buccal tablet, oral spray, or sublingual orally-administered formulation. Alternatively, the active ingredient may be incorporated into an oral solution such as one containing sodium borate, glycerin and potassium bicarbonate, or dispersed in a dentifrice, or added in a therapeutically-effective amount to a composition that may include water, binders, abrasives, flavoring agents, foaming agents, and humectants. Alternatively the compositions may be fashioned into a tablet or solution form that may be placed under the tongue or otherwise dissolved in the mouth.

In certain circumstances it will be desirable to deliver the pharmaceutical compositions disclosed herein parenterally, intravenously, intramuscularly, or even intraperitoneally. Such approaches are well known to the skilled artisan, some of which are further described, for example, in U. S. Patent 5,543,158; U. S. Patent 5,641,515 and U. S. Patent 5,399,363. In certain embodiments, solutions of the active compounds as free base or pharmacologically acceptable salts may be prepared in water suitably mixed with a surfactant, such as hydroxypropylcellulose. Dispersions may also be prepared in glycerol, liquid polyethylene glycols, and mixtures thereof and in oils. Under ordinary conditions of storage and use, these preparations generally will contain a preservative to prevent the growth of microorganisms.

Illustrative pharmaceutical forms suitable for injectable use include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions (for example, see U. S. Patent 5,466,468). In all cases the form must be sterile and must be fluid to the extent that easy syringability exists. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms, such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (*e.g.*, glycerol, propylene glycol, and liquid polyethylene glycol, and the like), suitable mixtures thereof, and/or vegetable oils. Proper fluidity may be maintained, for example, by the use of a coating, such as lecithin, by the maintenance of the required particle size in the case of dispersion and/or

by the use of surfactants. The prevention of the action of microorganisms can be facilitated by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, thimerosal, and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars or sodium chloride.

- 5 Prolonged absorption of the injectable compositions can be brought about by the use in the compositions of agents delaying absorption, for example, aluminum monostearate and gelatin.

In one embodiment, for parenteral administration in an aqueous solution, the solution should be suitably buffered if necessary and the liquid diluent first rendered  
10 isotonic with sufficient saline or glucose. These particular aqueous solutions are especially suitable for intravenous, intramuscular, subcutaneous and intraperitoneal administration. In this connection, a sterile aqueous medium that can be employed will be known to those of skill in the art in light of the present disclosure. For example, one dosage may be dissolved in 1 ml of isotonic NaCl solution and either added to 1000 ml  
15 of hypodermoclysis fluid or injected at the proposed site of infusion, (see for example, "Remington's Pharmaceutical Sciences" 15th Edition, pages 1035-1038 and 1570-1580). Some variation in dosage will necessarily occur depending on the condition of the subject being treated. Moreover, for human administration, preparations will of course preferably meet sterility, pyrogenicity, and the general safety and purity  
20 standards as required by FDA Office of Biologics standards.

In another embodiment of the invention, the compositions disclosed herein may be formulated in a neutral or salt form. Illustrative pharmaceutically-acceptable salts include the acid addition salts (formed with the free amino groups of the protein) and which are formed with inorganic acids such as, for  
25 example, hydrochloric or phosphoric acids, or such organic acids as acetic, oxalic, tartaric, mandelic, and the like. Salts formed with the free carboxyl groups can also be derived from inorganic bases such as, for example, sodium, potassium, ammonium, calcium, or ferric hydroxides, and such organic bases as isopropylamine, trimethylamine, histidine, procaine and the like. Upon formulation, solutions will be

administered in a manner compatible with the dosage formulation and in such amount as is therapeutically effective.

The carriers can further comprise any and all solvents, dispersion media, vehicles, coatings, diluents, antibacterial and antifungal agents, isotonic and absorption  
5 delaying agents, buffers, carrier solutions, suspensions, colloids, and the like. The use of such media and agents for pharmaceutical active substances is well known in the art. Except insofar as any conventional media or agent is incompatible with the active ingredient, its use in the therapeutic compositions is contemplated. Supplementary active ingredients can also be incorporated into the compositions. The phrase  
10 "pharmaceutically-acceptable" refers to molecular entities and compositions that do not produce an allergic or similar untoward reaction when administered to a human.

In certain embodiments, the pharmaceutical compositions may be delivered by intranasal sprays, inhalation, and/or other aerosol delivery vehicles. Methods for delivering genes, nucleic acids, and peptide compositions directly to the  
15 lungs *via* nasal aerosol sprays has been described, *e.g.*, in U. S. Patent 5,756,353 and U. S. Patent 5,804,212. Likewise, the delivery of drugs using intranasal microparticle resins (Takenaga *et al.*, J Controlled Release 1998 Mar 2;52(1-2):81-7) and lysophosphatidyl-glycerol compounds (U. S. Patent 5,725,871) are also well-known in the pharmaceutical arts. Likewise, illustrative transmucosal drug delivery in the form of  
20 a polytetrafluoroethylene support matrix is described in U. S. Patent 5,780,045.

In certain embodiments, liposomes, nanocapsules, microparticles, lipid particles, vesicles, and the like, are used for the introduction of the compositions of the present invention into suitable host cells/organisms. In particular, the compositions of the present invention may be formulated for delivery either encapsulated in a lipid  
25 particle, a liposome, a vesicle, a nanosphere, or a nanoparticle or the like. Alternatively, compositions of the present invention can be bound, either covalently or non-covalently, to the surface of such carrier vehicles.

The formation and use of liposome and liposome-like preparations as potential drug carriers is generally known to those of skill in the art (see for example,  
30 Lasic, Trends Biotechnol 1998 Jul;16(7):307-21; Takakura, Nippon Rinsho 1998

Mar;56(3):691-5; Chandran *et al.*, Indian J Exp Biol. 1997 Aug;35(8):801-9; Margalit, Crit Rev Ther Drug Carrier Syst. 1995;12(2-3):233-61; U.S. Patent 5,567,434; U.S. Patent 5,552,157; U.S. Patent 5,565,213; U.S. Patent 5,738,868 and U.S. Patent 5,795,587, each specifically incorporated herein by reference in its entirety).

5               Liposomes have been used successfully with a number of cell types that are normally difficult to transfect by other procedures, including T cell suspensions, primary hepatocyte cultures and PC 12 cells (Renneisen *et al.*, J Biol Chem. 1990 Sep 25;265(27):16337-42; Muller *et al.*, DNA Cell Biol. 1990 Apr;9(3):221-9). In addition, liposomes are free of the DNA length constraints that are typical of viral-based delivery  
10 systems. Liposomes have been used effectively to introduce genes, various drugs, radiotherapeutic agents, enzymes, viruses, transcription factors, allosteric effectors and the like, into a variety of cultured cell lines and animals. Furthermore, the use of liposomes does not appear to be associated with autoimmune responses or unacceptable toxicity after systemic delivery.

15               In certain embodiments, liposomes are formed from phospholipids that are dispersed in an aqueous medium and spontaneously form multilamellar concentric bilayer vesicles (also termed multilamellar vesicles (MLVs)).

              Alternatively, in other embodiments, the invention provides for pharmaceutically-acceptable nanocapsule formulations of the compositions of the  
20 present invention. Nanocapsules can generally entrap compounds in a stable and reproducible way (see, for example, Quintanar-Guerrero *et al.*, Drug Dev Ind Pharm. 1998 Dec;24(12):1113-28). To avoid side effects due to intracellular polymeric overloading, such ultrafine particles (sized around 0.1  $\mu$ m) may be designed using polymers able to be degraded *in vivo*. Such particles can be made as described, for  
25 example, by Couvreur *et al.*, Crit Rev Ther Drug Carrier Syst. 1988;5(1):1-20; zur Muhlen *et al.*, Eur J Pharm Biopharm. 1998 Mar;45(2):149-55; Zambaux *et al.* J Controlled Release. 1998 Jan 2;50(1-3):31-40; and U. S. Patent 5,145,684.

### Cancer Therapeutic Methods

In further aspects of the present invention, the pharmaceutical compositions described herein may be used for the treatment of cancer, particularly for the immunotherapy of prostate cancer. Within such methods, the pharmaceutical compositions described herein are administered to a patient, typically a warm-blooded animal, preferably a human. A patient may or may not be afflicted with cancer. Accordingly, the above pharmaceutical compositions may be used to prevent the development of a cancer or to treat a patient afflicted with a cancer. Pharmaceutical compositions and vaccines may be administered either prior to or following surgical removal of primary tumors and/or treatment such as administration of radiotherapy or conventional chemotherapeutic drugs. As discussed above, administration of the pharmaceutical compositions may be by any suitable method, including administration by intravenous, intraperitoneal, intramuscular, subcutaneous, intranasal, intradermal, anal, vaginal, topical and oral routes.

Within certain embodiments, immunotherapy may be active immunotherapy, in which treatment relies on the *in vivo* stimulation of the endogenous host immune system to react against tumors with the administration of immune response-modifying agents (such as polypeptides and polynucleotides as provided herein).

Within other embodiments, immunotherapy may be passive immunotherapy, in which treatment involves the delivery of agents with established tumor-immune reactivity (such as effector cells or antibodies) that can directly or indirectly mediate antitumor effects and does not necessarily depend on an intact host immune system. Examples of effector cells include T cells as discussed above, T lymphocytes (such as CD8<sup>+</sup> cytotoxic T lymphocytes and CD4<sup>+</sup> T-helper tumor-infiltrating lymphocytes), killer cells (such as Natural Killer cells and lymphokine-activated killer cells), B cells and antigen-presenting cells (such as dendritic cells and macrophages) expressing a polypeptide provided herein. T cell receptors and antibody receptors specific for the polypeptides recited herein may be cloned, expressed and transferred into other vectors or effector cells for adoptive immunotherapy. The

polypeptides provided herein may also be used to generate antibodies or anti-idiotypic antibodies (as described above and in U.S. Patent No. 4,918,164) for passive immunotherapy.

Effector cells may generally be obtained in sufficient quantities for adoptive immunotherapy by growth *in vitro*, as described herein. Culture conditions for expanding single antigen-specific effector cells to several billion in number with retention of antigen recognition *in vivo* are well known in the art. Such *in vitro* culture conditions typically use intermittent stimulation with antigen, often in the presence of cytokines (such as IL-2) and non-dividing feeder cells. As noted above, immunoreactive polypeptides as provided herein may be used to rapidly expand antigen-specific T cell cultures in order to generate a sufficient number of cells for immunotherapy. In particular, antigen-presenting cells, such as dendritic, macrophage, monocyte, fibroblast and/or B cells, may be pulsed with immunoreactive polypeptides or transfected with one or more polynucleotides using standard techniques well known in the art. For example, antigen-presenting cells can be transfected with a polynucleotide having a promoter appropriate for increasing expression in a recombinant virus or other expression system. Cultured effector cells for use in therapy must be able to grow and distribute widely, and to survive long term *in vivo*. Studies have shown that cultured effector cells can be induced to grow *in vivo* and to survive long term in substantial numbers by repeated stimulation with antigen supplemented with IL-2 (*see, for example, Cheever et al., Immunological Reviews 157:177, 1997*).

Alternatively, a vector expressing a polypeptide recited herein may be introduced into antigen presenting cells taken from a patient and clonally propagated *ex vivo* for transplant back into the same patient. Transfected cells may be reintroduced into the patient using any means known in the art, preferably in sterile form by intravenous, intracavitary, intraperitoneal or intratumor administration.

Routes and frequency of administration of the therapeutic compositions described herein, as well as dosage, will vary from individual to individual, and may be readily established using standard techniques. In general, the pharmaceutical compositions and vaccines may be administered by injection (*e.g., intracutaneous,*

intramuscular, intravenous or subcutaneous), intranasally (*e.g.* by aspiration) or orally. Preferably, between 1 and 10 doses may be administered over a 52 week period. Preferably, 6 doses are administered, at intervals of 1 month, and booster vaccinations may be given periodically thereafter. Alternate protocols may be appropriate for individual patients. A suitable dose is an amount of a compound that, when administered as described above, is capable of promoting an anti-tumor immune response, and is at least 10-50% above the basal (*i.e.*, untreated) level. Such response can be monitored by measuring the anti-tumor antibodies in a patient or by vaccine-dependent generation of cytolytic effector cells capable of killing the patient's tumor cells *in vitro*. Such vaccines should also be capable of causing an immune response that leads to an improved clinical outcome (*e.g.*, more frequent remissions, complete or partial or longer disease-free survival) in vaccinated patients as compared to non-vaccinated patients. In general, for pharmaceutical compositions and vaccines comprising one or more polypeptides, the amount of each polypeptide present in a dose ranges from about 25 µg to 5 mg per kg of host. Suitable dose sizes will vary with the size of the patient, but will typically range from about 0.1 mL to about 5 mL.

In general, an appropriate dosage and treatment regimen provides the active compound(s) in an amount sufficient to provide therapeutic and/or prophylactic benefit. Such a response can be monitored by establishing an improved clinical outcome (*e.g.*, more frequent remissions, complete or partial, or longer disease-free survival) in treated patients as compared to non-treated patients. Increases in preexisting immune responses to a tumor protein generally correlate with an improved clinical outcome. Such immune responses may generally be evaluated using standard proliferation, cytotoxicity or cytokine assays, which may be performed using samples obtained from a patient before and after treatment.

#### Cancer Detection and Diagnostic Compositions, Methods and Kits

In general, a cancer may be detected in a patient based on the presence of one or more prostate tumor proteins and/or polynucleotides encoding such proteins in a biological sample (for example, blood, sera, sputum urine and/or tumor biopsies)

obtained from the patient. In other words, such proteins may be used as markers to indicate the presence or absence of a cancer such as prostate cancer. In addition, such proteins may be useful for the detection of other cancers. The binding agents provided herein generally permit detection of the level of antigen that binds to the agent in the biological sample. Polynucleotide primers and probes may be used to detect the level of mRNA encoding a tumor protein, which is also indicative of the presence or absence of a cancer. In general, a prostate tumor sequence should be present at a level that is at least three fold higher in tumor tissue than in normal tissue

There are a variety of assay formats known to those of ordinary skill in the art for using a binding agent to detect polypeptide markers in a sample. *See, e.g.,* Harlow and Lane, *Antibodies: A Laboratory Manual*, Cold Spring Harbor Laboratory, 1988. In general, the presence or absence of a cancer in a patient may be determined by (a) contacting a biological sample obtained from a patient with a binding agent; (b) detecting in the sample a level of polypeptide that binds to the binding agent; and (c) comparing the level of polypeptide with a predetermined cut-off value.

In a preferred embodiment, the assay involves the use of binding agent immobilized on a solid support to bind to and remove the polypeptide from the remainder of the sample. The bound polypeptide may then be detected using a detection reagent that contains a reporter group and specifically binds to the binding agent/polypeptide complex. Such detection reagents may comprise, for example, a binding agent that specifically binds to the polypeptide or an antibody or other agent that specifically binds to the binding agent, such as an anti-immunoglobulin, protein G, protein A or a lectin. Alternatively, a competitive assay may be utilized, in which a polypeptide is labeled with a reporter group and allowed to bind to the immobilized binding agent after incubation of the binding agent with the sample. The extent to which components of the sample inhibit the binding of the labeled polypeptide to the binding agent is indicative of the reactivity of the sample with the immobilized binding agent. Suitable polypeptides for use within such assays include full length prostate tumor proteins and polypeptide portions thereof to which the binding agent binds, as described above.



The solid support may be any material known to those of ordinary skill in the art to which the tumor protein may be attached. For example, the solid support may be a test well in a microtiter plate or a nitrocellulose or other suitable membrane. Alternatively, the support may be a bead or disc, such as glass, fiberglass, latex or a plastic material such as polystyrene or polyvinylchloride. The support may also be a magnetic particle or a fiber optic sensor, such as those disclosed, for example, in U.S. Patent No. 5,359,681. The binding agent may be immobilized on the solid support using a variety of techniques known to those of skill in the art, which are amply described in the patent and scientific literature. In the context of the present invention, the term "immobilization" refers to both noncovalent association, such as adsorption, and covalent attachment (which may be a direct linkage between the agent and functional groups on the support or may be a linkage by way of a cross-linking agent). Immobilization by adsorption to a well in a microtiter plate or to a membrane is preferred. In such cases, adsorption may be achieved by contacting the binding agent, in a suitable buffer, with the solid support for a suitable amount of time. The contact time varies with temperature, but is typically between about 1 hour and about 1 day. In general, contacting a well of a plastic microtiter plate (such as polystyrene or polyvinylchloride) with an amount of binding agent ranging from about 10 ng to about 10  $\mu$ g, and preferably about 100 ng to about 1  $\mu$ g, is sufficient to immobilize an adequate amount of binding agent.

Covalent attachment of binding agent to a solid support may generally be achieved by first reacting the support with a bifunctional reagent that will react with both the support and a functional group, such as a hydroxyl or amino group, on the binding agent. For example, the binding agent may be covalently attached to supports having an appropriate polymer coating using benzoquinone or by condensation of an aldehyde group on the support with an amine and an active hydrogen on the binding partner (*see, e.g.,* Pierce Immunotechnology Catalog and Handbook, 1991, at A12-A13).

In certain embodiments, the assay is a two-antibody sandwich assay. This assay may be performed by first contacting an antibody that has been immobilized

on a solid support, commonly the well of a microtiter plate, with the sample, such that polypeptides within the sample are allowed to bind to the immobilized antibody. Unbound sample is then removed from the immobilized polypeptide-antibody complexes and a detection reagent (preferably a second antibody capable of binding to a different site on the polypeptide) containing a reporter group is added. The amount of detection reagent that remains bound to the solid support is then determined using a method appropriate for the specific reporter group.

More specifically, once the antibody is immobilized on the support as described above, the remaining protein binding sites on the support are typically blocked. Any suitable blocking agent known to those of ordinary skill in the art, such as bovine serum albumin or Tween 20<sup>TM</sup> (Sigma Chemical Co., St. Louis, MO). The immobilized antibody is then incubated with the sample, and polypeptide is allowed to bind to the antibody. The sample may be diluted with a suitable diluent, such as phosphate-buffered saline (PBS) prior to incubation. In general, an appropriate contact time (*i.e.*, incubation time) is a period of time that is sufficient to detect the presence of polypeptide within a sample obtained from an individual with prostate cancer. Preferably, the contact time is sufficient to achieve a level of binding that is at least about 95% of that achieved at equilibrium between bound and unbound polypeptide. Those of ordinary skill in the art will recognize that the time necessary to achieve equilibrium may be readily determined by assaying the level of binding that occurs over a period of time. At room temperature, an incubation time of about 30 minutes is generally sufficient.

Unbound sample may then be removed by washing the solid support with an appropriate buffer, such as PBS containing 0.1% Tween 20<sup>TM</sup>. The second antibody, which contains a reporter group, may then be added to the solid support. Preferred reporter groups include those groups recited above.

The detection reagent is then incubated with the immobilized antibody-polypeptide complex for an amount of time sufficient to detect the bound polypeptide. An appropriate amount of time may generally be determined by assaying the level of binding that occurs over a period of time. Unbound detection reagent is then removed

and bound detection reagent is detected using the reporter group. The method employed for detecting the reporter group depends upon the nature of the reporter group. For radioactive groups, scintillation counting or autoradiographic methods are generally appropriate. Spectroscopic methods may be used to detect dyes, luminescent groups and fluorescent groups. Biotin may be detected using avidin, coupled to a different reporter group (commonly a radioactive or fluorescent group or an enzyme). Enzyme reporter groups may generally be detected by the addition of substrate (generally for a specific period of time), followed by spectroscopic or other analysis of the reaction products.

10 To determine the presence or absence of a cancer, such as prostate cancer, the signal detected from the reporter group that remains bound to the solid support is generally compared to a signal that corresponds to a predetermined cut-off value. In one preferred embodiment, the cut-off value for the detection of a cancer is the average mean signal obtained when the immobilized antibody is incubated with  
15 samples from patients without the cancer. In general, a sample generating a signal that is three standard deviations above the predetermined cut-off value is considered positive for the cancer. In an alternate preferred embodiment, the cut-off value is determined using a Receiver Operator Curve, according to the method of Sackett et al., *Clinical Epidemiology: A Basic Science for Clinical Medicine*, Little Brown and Co., 1985,  
20 p. 106-7. Briefly, in this embodiment, the cut-off value may be determined from a plot of pairs of true positive rates (*i.e.*, sensitivity) and false positive rates (100%-specificity) that correspond to each possible cut-off value for the diagnostic test result. The cut-off value on the plot that is the closest to the upper left-hand corner (*i.e.*, the value that encloses the largest area) is the most accurate cut-off value, and a sample generating a  
25 signal that is higher than the cut-off value determined by this method may be considered positive. Alternatively, the cut-off value may be shifted to the left along the plot, to minimize the false positive rate, or to the right, to minimize the false negative rate. In general, a sample generating a signal that is higher than the cut-off value determined by this method is considered positive for a cancer.

In a related embodiment, the assay is performed in a flow-through or strip test format, wherein the binding agent is immobilized on a membrane, such as nitrocellulose. In the flow-through test, polypeptides within the sample bind to the immobilized binding agent as the sample passes through the membrane. A second, labeled binding agent then binds to the binding agent-polypeptide complex as a solution containing the second binding agent flows through the membrane. The detection of bound second binding agent may then be performed as described above. In the strip test format, one end of the membrane to which binding agent is bound is immersed in a solution containing the sample. The sample migrates along the membrane through a region containing second binding agent and to the area of immobilized binding agent. Concentration of second binding agent at the area of immobilized antibody indicates the presence of a cancer. Typically, the concentration of second binding agent at that site generates a pattern, such as a line, that can be read visually. The absence of such a pattern indicates a negative result. In general, the amount of binding agent immobilized on the membrane is selected to generate a visually discernible pattern when the biological sample contains a level of polypeptide that would be sufficient to generate a positive signal in the two-antibody sandwich assay, in the format discussed above. Preferred binding agents for use in such assays are antibodies and antigen-binding fragments thereof. Preferably, the amount of antibody immobilized on the membrane ranges from about 25 ng to about 1  $\mu$ g, and more preferably from about 50 ng to about 500 ng. Such tests can typically be performed with a very small amount of biological sample.

Of course, numerous other assay protocols exist that are suitable for use with the tumor proteins or binding agents of the present invention. The above descriptions are intended to be exemplary only. For example, it will be apparent to those of ordinary skill in the art that the above protocols may be readily modified to use tumor polypeptides to detect antibodies that bind to such polypeptides in a biological sample. The detection of such tumor protein specific antibodies may correlate with the presence of a cancer.

A cancer may also, or alternatively, be detected based on the presence of T cells that specifically react with a tumor protein in a biological sample. Within certain methods, a biological sample comprising CD4<sup>+</sup> and/or CD8<sup>+</sup> T cells isolated from a patient is incubated with a tumor polypeptide, a polynucleotide encoding such a polypeptide and/or an APC that expresses at least an immunogenic portion of such a polypeptide, and the presence or absence of specific activation of the T cells is detected. Suitable biological samples include, but are not limited to, isolated T cells. For example, T cells may be isolated from a patient by routine techniques (such as by Ficoll/Hypaque density gradient centrifugation of peripheral blood lymphocytes). T cells may be incubated *in vitro* for 2-9 days (typically 4 days) at 37°C with polypeptide (e.g., 5 - 25 µg/ml). It may be desirable to incubate another aliquot of a T cell sample in the absence of tumor polypeptide to serve as a control. For CD4<sup>+</sup> T cells, activation is preferably detected by evaluating proliferation of the T cells. For CD8<sup>+</sup> T cells, activation is preferably detected by evaluating cytolytic activity. A level of proliferation that is at least two fold greater and/or a level of cytolytic activity that is at least 20% greater than in disease-free patients indicates the presence of a cancer in the patient.

As noted above, a cancer may also, or alternatively, be detected based on the level of mRNA encoding a tumor protein in a biological sample. For example, at least two oligonucleotide primers may be employed in a polymerase chain reaction (PCR) based assay to amplify a portion of a tumor cDNA derived from a biological sample, wherein at least one of the oligonucleotide primers is specific for (*i.e.*, hybridizes to) a polynucleotide encoding the tumor protein. The amplified cDNA is then separated and detected using techniques well known in the art, such as gel electrophoresis. Similarly, oligonucleotide probes that specifically hybridize to a polynucleotide encoding a tumor protein may be used in a hybridization assay to detect the presence of polynucleotide encoding the tumor protein in a biological sample.

To permit hybridization under assay conditions, oligonucleotide primers and probes should comprise an oligonucleotide sequence that has at least about 60%, preferably at least about 75% and more preferably at least about 90%, identity to a portion of a polynucleotide encoding a tumor protein of the invention that is at least 10

nucleotides, and preferably at least 20 nucleotides, in length. Preferably, oligonucleotide primers and/or probes hybridize to a polynucleotide encoding a polypeptide described herein under moderately stringent conditions, as defined above. Oligonucleotide primers and/or probes which may be usefully employed in the  
5 diagnostic methods described herein preferably are at least 10-40 nucleotides in length. In a preferred embodiment, the oligonucleotide primers comprise at least 10 contiguous nucleotides, more preferably at least 15 contiguous nucleotides, of a DNA molecule having a sequence as disclosed herein. Techniques for both PCR based assays and hybridization assays are well known in the art (*see*, for example, Mullis et al., *Cold*  
10 *Spring Harbor Symp. Quant. Biol.*, 51:263, 1987; Erlich ed., *PCR Technology*, Stockton Press, NY, 1989).

One preferred assay employs RT-PCR, in which PCR is applied in conjunction with reverse transcription. Typically, RNA is extracted from a biological sample, such as biopsy tissue, and is reverse transcribed to produce cDNA molecules.  
15 PCR amplification using at least one specific primer generates a cDNA molecule, which may be separated and visualized using, for example, gel electrophoresis. Amplification may be performed on biological samples taken from a test patient and from an individual who is not afflicted with a cancer. The amplification reaction may be performed on several dilutions of cDNA spanning two orders of magnitude. A two-fold  
20 or greater increase in expression in several dilutions of the test patient sample as compared to the same dilutions of the non-cancerous sample is typically considered positive.

In another embodiment, the compositions described herein may be used as markers for the progression of cancer. In this embodiment, assays as described above  
25 for the diagnosis of a cancer may be performed over time, and the change in the level of reactive polypeptide(s) or polynucleotide(s) evaluated. For example, the assays may be performed every 24-72 hours for a period of 6 months to 1 year, and thereafter performed as needed. In general, a cancer is progressing in those patients in whom the level of polypeptide or polynucleotide detected increases over time. In contrast, the

cancer is not progressing when the level of reactive polypeptide or polynucleotide either remains constant or decreases with time.

Certain *in vivo* diagnostic assays may be performed directly on a tumor. One such assay involves contacting tumor cells with a binding agent. The bound  
5 binding agent may then be detected directly or indirectly via a reporter group. Such binding agents may also be used in histological applications. Alternatively, polynucleotide probes may be used within such applications.

As noted above, to improve sensitivity, multiple tumor protein markers may be assayed within a given sample. It will be apparent that binding agents specific  
10 for different proteins provided herein may be combined within a single assay. Further, multiple primers or probes may be used concurrently. The selection of tumor protein markers may be based on routine experiments to determine combinations that results in optimal sensitivity. In addition, or alternatively, assays for tumor proteins provided herein may be combined with assays for other known tumor antigens.

15 The present invention further provides kits for use within any of the above diagnostic methods. Such kits typically comprise two or more components necessary for performing a diagnostic assay. Components may be compounds, reagents, containers and/or equipment. For example, one container within a kit may contain a monoclonal antibody or fragment thereof that specifically binds to a tumor protein.  
20 Such antibodies or fragments may be provided attached to a support material, as described above. One or more additional containers may enclose elements, such as reagents or buffers, to be used in the assay. Such kits may also, or alternatively, contain a detection reagent as described above that contains a reporter group suitable for direct or indirect detection of antibody binding.

25 Alternatively, a kit may be designed to detect the level of mRNA encoding a tumor protein in a biological sample. Such kits generally comprise at least one oligonucleotide probe or primer, as described above, that hybridizes to a polynucleotide encoding a tumor protein. Such an oligonucleotide may be used, for example, within a PCR or hybridization assay. Additional components that may be

present within such kits include a second oligonucleotide and/or a diagnostic reagent or container to facilitate the detection of a polynucleotide encoding a tumor protein.

The following Examples are offered by way of illustration and not by way of limitation.

5

## EXAMPLES

### EXAMPLE 1

#### ISOLATION AND CHARACTERIZATION OF PROSTATE-SPECIFIC POLYPEPTIDES

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This Example describes the isolation of certain prostate-specific polypeptides from a prostate tumor cDNA library.

A human prostate tumor cDNA expression library was constructed from prostate tumor poly A<sup>+</sup> RNA using a Superscript Plasmid System for cDNA Synthesis and Plasmid Cloning kit (BRL Life Technologies, Gaithersburg, MD 20897) following the manufacturer's protocol. Specifically, prostate tumor tissues were homogenized with polytron (Kinematica, Switzerland) and total RNA was extracted using Trizol reagent (BRL Life Technologies) as directed by the manufacturer. The poly A<sup>+</sup> RNA was then purified using a Qiagen oligotex spin column mRNA purification kit (Qiagen, Santa Clarita, CA 91355) according to the manufacturer's protocol. First-strand cDNA was synthesized using the NotI/Oligo-dT18 primer. Double-stranded cDNA was synthesized, ligated with EcoRI/BAXI adaptors (Invitrogen, San Diego, CA) and digested with NotI. Following size fractionation with Chroma Spin-1000 columns (Clontech, Palo Alto, CA), the cDNA was ligated into the EcoRI/NotI site of pCDNA3.1 (Invitrogen) and transformed into ElectroMax *E. coli* DH10B cells (BRL Life Technologies) by electroporation.

Using the same procedure, a normal human pancreas cDNA expression library was prepared from a pool of six tissue specimens (Clontech). The cDNA libraries were characterized by determining the number of independent colonies, the percentage of clones that carried insert, the average insert size and by sequence analysis.

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The prostate tumor library contained  $1.64 \times 10^7$  independent colonies, with 70% of clones having an insert and the average insert size being 1745 base pairs. The normal pancreas cDNA library contained  $3.3 \times 10^6$  independent colonies, with 69% of clones having inserts and the average insert size being 1120 base pairs. For both libraries, sequence analysis showed that the majority of clones had a full length cDNA sequence and were synthesized from mRNA, with minimal rRNA and mitochondrial DNA contamination.

cDNA library subtraction was performed using the above prostate tumor and normal pancreas cDNA libraries, as described by Hara *et al.* (*Blood*, 84:189-199, 1994) with some modifications. Specifically, a prostate tumor-specific subtracted cDNA library was generated as follows. Normal pancreas cDNA library (70  $\mu$ g) was digested with EcoRI, NotI, and SfuI, followed by a filling-in reaction with DNA polymerase Klenow fragment. After phenol-chloroform extraction and ethanol precipitation, the DNA was dissolved in 100  $\mu$ l of H<sub>2</sub>O, heat-denatured and mixed with 100  $\mu$ l (100  $\mu$ g) of Photoprobe biotin (Vector Laboratories, Burlingame, CA). As recommended by the manufacturer, the resulting mixture was irradiated with a 270 W sunlamp on ice for 20 minutes. Additional Photoprobe biotin (50  $\mu$ l) was added and the biotinylation reaction was repeated. After extraction with butanol five times, the DNA was ethanol-precipitated and dissolved in 23  $\mu$ l H<sub>2</sub>O to form the driver DNA.

To form the tracer DNA, 10  $\mu$ g prostate tumor cDNA library was digested with BamHI and XhoI, phenol chloroform extracted and passed through Chroma spin-400 columns (Clontech). Following ethanol precipitation, the tracer DNA was dissolved in 5  $\mu$ l H<sub>2</sub>O. Tracer DNA was mixed with 15  $\mu$ l driver DNA and 20  $\mu$ l of 2 x hybridization buffer (1.5 M NaCl/10 mM EDTA/50 mM HEPES pH 7.5/0.2% sodium dodecyl sulfate), overlaid with mineral oil, and heat-denatured completely. The sample was immediately transferred into a 68 °C water bath and incubated for 20 hours (long hybridization [LH]). The reaction mixture was then subjected to a streptavidin treatment followed by phenol/chloroform extraction. This process was repeated three more times. Subtracted DNA was precipitated, dissolved in 12  $\mu$ l H<sub>2</sub>O, mixed with 8  $\mu$ l driver DNA and 20  $\mu$ l of 2 x hybridization buffer, and subjected to a hybridization at 68

$^{32}$ P for 2 hours (short hybridization [SH]). After removal of biotinylated double-stranded DNA, subtracted cDNA was ligated into BamHI/XhoI site of chloramphenicol resistant pBCSK<sup>+</sup> (Stratagene, La Jolla, CA 92037) and transformed into ElectroMax *E. coli* DH10B cells by electroporation to generate a prostate tumor specific subtracted  
5 cDNA library (referred to as "prostate subtraction 1").

To analyze the subtracted cDNA library, plasmid DNA was prepared from 100 independent clones, randomly picked from the subtracted prostate tumor specific library and grouped based on insert size. Representative cDNA clones were further characterized by DNA sequencing with a Perkin Elmer/Applied Biosystems  
10 Division Automated Sequencer Model 373A (Foster City, CA). Six cDNA clones, hereinafter referred to as F1-13, F1-12, F1-16, H1-1, H1-9 and H1-4, were shown to be abundant in the subtracted prostate-specific cDNA library. The determined 3' and 5' cDNA sequences for F1-12 are provided in SEQ ID NO: 2 and 3, respectively, with determined 3' cDNA sequences for F1-13, F1-16, H1-1, H1-9 and H1-4 being provided  
15 in SEQ ID NO: 1 and 4-7, respectively.

The cDNA sequences for the isolated clones were compared to known sequences in the gene bank using the EMBL and GenBank databases (release 96). Four of the prostate tumor cDNA clones, F1-13, F1-16, H1-1, and H1-4, were determined to encode the following previously identified proteins: prostate specific antigen (PSA),  
20 human glandular kallikrein, human tumor expression enhanced gene, and mitochondria cytochrome C oxidase subunit II. H1-9 was found to be identical to a previously identified human autonomously replicating sequence. No significant homologies to the cDNA sequence for F1-12 were found.

Subsequent studies led to the isolation of a full-length cDNA sequence  
25 for F1-12 (also referred to as P504S). This sequence is provided in SEQ ID NO: 107, with the corresponding predicted amino acid sequence being provided in SEQ ID NO: 108. cDNA splice variants of P504S are provided in SEQ ID NO: 600-605.

To clone less abundant prostate tumor specific genes, cDNA library subtraction was performed by subtracting the prostate tumor cDNA library described  
30 above with the normal pancreas cDNA library and with the three most abundant genes

in the previously subtracted prostate tumor specific cDNA library: human glandular kallikrein, prostate specific antigen (PSA), and mitochondria cytochrome C oxidase subunit II. Specifically, 1  $\mu$ g each of human glandular kallikrein, PSA and mitochondria cytochrome C oxidase subunit II cDNAs in pCDNA3.1 were added to the  
5 driver DNA and subtraction was performed as described above to provide a second subtracted cDNA library hereinafter referred to as the "subtracted prostate tumor specific cDNA library with spike".

Twenty-two cDNA clones were isolated from the subtracted prostate tumor specific cDNA library with spike. The determined 3' and 5' cDNA sequences for  
10 the clones referred to as J1-17, L1-12, N1-1862, J1-13, J1-19, J1-25, J1-24, K1-58, K1-63, L1-4 and L1-14 are provided in SEQ ID NOS: 8-9, 10-11, 12-13, 14-15, 16-17, 18-19, 20-21, 22-23, 24-25, 26-27 and 28-29, respectively. The determined 3' cDNA sequences for the clones referred to as J1-12, J1-16, J1-21, K1-48, K1-55, L1-2, L1-6, N1-1858, N1-1860, N1-1861, N1-1864 are provided in SEQ ID NOS: 30-40,  
15 respectively. Comparison of these sequences with those in the gene bank as described above, revealed no significant homologies to three of the five most abundant DNA species, (J1-17, L1-12 and N1-1862; SEQ ID NOS: 8-9, 10-11 and 12-13, respectively). Of the remaining two most abundant species, one (J1-12; SEQ ID NO:30) was found to be identical to the previously identified human pulmonary surfactant-associated protein,  
20 and the other (K1-48; SEQ ID NO:33) was determined to have some homology to *R. norvegicus* mRNA for 2-arylpropionyl-CoA epimerase. Of the 17 less abundant cDNA clones isolated from the subtracted prostate tumor specific cDNA library with spike, four (J1-16, K1-55, L1-6 and N1-1864; SEQ ID NOS:31, 34, 36 and 40, respectively) were found to be identical to previously identified sequences, two (J1-21 and N1-1860;  
25 SEQ ID NOS: 32 and 38, respectively) were found to show some homology to non-human sequences, and two (L1-2 and N1-1861; SEQ ID NOS: 35 and 39, respectively) were found to show some homology to known human sequences. No significant homologies were found to the polypeptides J1-13, J1-19, J1-24, J1-25, K1-58, K1-63, L1-4, L1-14 (SEQ ID NOS: 14-15, 16-17, 20-21, 18-19, 22-23, 24-25, 26-27, 28-29,  
30 respectively).

Subsequent studies led to the isolation of full length cDNA sequences for J1-17, L1-12 and N1-1862 (SEQ ID NOS: 109-111, respectively). The corresponding predicted amino acid sequences are provided in SEQ ID NOS: 112-114. L1-12 is also referred to as P501S. A cDNA splice variant of P501S is provided in SEQ ID NO: 606.

- 5           In a further experiment, four additional clones were identified by subtracting a prostate tumor cDNA library with normal prostate cDNA prepared from a pool of three normal prostate poly A+ RNA (referred to as "prostate subtraction 2"). The determined cDNA sequences for these clones, hereinafter referred to as U1-3064, U1-3065, V1-3692 and 1A-3905, are provided in SEQ ID NO: 69-72, respectively.
- 10   Comparison of the determined sequences with those in the gene bank revealed no significant homologies to U1-3065.

- A second subtraction with spike (referred to as "prostate subtraction spike 2") was performed by subtracting a prostate tumor specific cDNA library with spike with normal pancreas cDNA library and further spiked with PSA, J1-17,
- 15   pulmonary surfactant-associated protein, mitochondrial DNA, cytochrome c oxidase subunit II, N1-1862, autonomously replicating sequence, L1-12 and tumor expression enhanced gene. Four additional clones, hereinafter referred to as V1-3686, R1-2330, 1B-3976 and V1-3679, were isolated. The determined cDNA sequences for these clones are provided in SEQ ID NO:73-76, respectively. Comparison of these sequences
- 20   with those in the gene bank revealed no significant homologies to V1-3686 and R1-2330.

- Further analysis of the three prostate subtractions described above (prostate subtraction 2, subtracted prostate tumor specific cDNA library with spike, and prostate subtraction spike 2) resulted in the identification of sixteen additional clones,
- 25   referred to as 1G-4736, 1G-4738, 1G-4741, 1G-4744, 1G-4734, 1H-4774, 1H-4781, 1H-4785, 1H-4787, 1H-4796, 1I-4810, 1I-4811, 1J-4876, 1K-4884 and 1K-4896. The determined cDNA sequences for these clones are provided in SEQ ID NOS: 77-92, respectively. Comparison of these sequences with those in the gene bank as described above, revealed no significant homologies to 1G-4741, 1G-4734, 1I-4807, 1J-4876 and
- 30   1K-4896 (SEQ ID NOS: 79, 81, 87, 90 and 92, respectively). Further analysis of the

isolated clones led to the determination of extended cDNA sequences for 1G-4736, 1G-4738, 1G-4741, 1G-4744, 1H-4774, 1H-4781, 1H-4785, 1H-4787, 1H-4796, 1I-4807, 1J-4876, 1K-4884 and 1K-4896, provided in SEQ ID NOS: 179-188 and 191-193, respectively, and to the determination of additional partial cDNA sequences for 1I-4810  
5 and 1I-4811, provided in SEQ ID NOS: 189 and 190, respectively.

Additional studies with prostate subtraction spike 2 resulted in the isolation of three more clones. Their sequences were determined as described above and compared to the most recent GenBank. All three clones were found to have homology to known genes, which are Cysteine-rich protein, KIAA0242, and KIAA0280  
10 (SEQ ID NO: 317, 319, and 320, respectively). Further analysis of these clones by Synteni microarray (Synteni, Palo Alto, CA) demonstrated that all three clones were over-expressed in most prostate tumors and prostate BPH, as well as in the majority of normal prostate tissues tested, but low expression in all other normal tissues.

An additional subtraction was performed by subtracting a normal  
15 prostate cDNA library with normal pancreas cDNA (referred to as "prostate subtraction 3"). This led to the identification of six additional clones referred to as 1G-4761, 1G-4762, 1H-4766, 1H-4770, 1H-4771 and 1H-4772 (SEQ ID NOS: 93-98). Comparison of these sequences with those in the gene bank revealed no significant homologies to 1G-4761 and 1H-4771 (SEQ ID NOS: 93 and 97, respectively). Further analysis of the  
20 isolated clones led to the determination of extended cDNA sequences for 1G-4761, 1G-4762, 1H-4766 and 1H-4772 provided in SEQ ID NOS: 194-196 and 199, respectively, and to the determination of additional partial cDNA sequences for 1H-4770 and 1H-4771, provided in SEQ ID NOS: 197 and 198, respectively.

Subtraction of a prostate tumor cDNA library, prepared from a pool of  
25 polyA+ RNA from three prostate cancer patients, with a normal pancreas cDNA library (prostate subtraction 4) led to the identification of eight clones, referred to as 1D-4297, 1D-4309, 1D-4278, 1D-4288, 1D-4283, 1D-4304, 1D-4296 and 1D-4280 (SEQ ID NOS: 99-107). These sequences were compared to those in the gene bank as described above. No significant homologies were found to 1D-4283 and 1D-4304 (SEQ ID NOS:  
30 103 and 104, respectively). Further analysis of the isolated clones led to the

determination of extended cDNA sequences for 1D-4309, 1D-4278, 1D-4288, 1D-4283, 1D-4304, 1D-4296 and 1D-4280, provided in SEQ ID NOS: 200-206, respectively.

cDNA clones isolated in prostate subtraction 1 and prostate subtraction  
5 2, described above, were colony PCR amplified and their mRNA expression levels in prostate tumor, normal prostate and in various other normal tissues were determined using microarray technology (Synteni, Palo Alto, CA). Briefly, the PCR amplification products were dotted onto slides in an array format, with each product occupying a unique location in the array. mRNA was extracted from the tissue sample to be tested,  
10 reverse transcribed, and fluorescent-labeled cDNA probes were generated. The microarrays were probed with the labeled cDNA probes, the slides scanned and fluorescence intensity was measured. This intensity correlates with the hybridization intensity. Two clones (referred to as P509S and P510S) were found to be over-expressed in prostate tumor and normal prostate and expressed at low levels in all other  
15 normal tissues tested (liver, pancreas, skin, bone marrow, brain, breast, adrenal gland, bladder, testes, salivary gland, large intestine, kidney, ovary, lung, spinal cord, skeletal muscle and colon). The determined cDNA sequences for P509S and P510S are provided in SEQ ID NO: 223 and 224, respectively. Comparison of these sequences with those in the gene bank as described above, revealed some homology to previously  
20 identified ESTs.

Additional, studies led to the isolation of the full-length cDNA sequence for P509S. This sequence is provided in SEQ ID NO: 332, with the corresponding predicted amino acid sequence being provided in SEQ ID NO: 339. Two variant full-length cDNA sequences for P510S are provided in SEQ ID NO: 535 and 536, with the  
25 corresponding predicted amino acid sequences being provided in SEQ ID NO: 537 and 538, respectively. Additional splice variants of P510S are provided in SEQ ID NO: 598 and 599.

## EXAMPLE 2

## DETERMINATION OF TISSUE SPECIFICITY OF PROSTATE-SPECIFIC POLYPEPTIDES

Using gene specific primers, mRNA expression levels for the  
5 representative prostate-specific polypeptides F1-16, H1-1, J1-17 (also referred to as P502S), L1-12 (also referred to as P501S), F1-12 (also referred to as P504S) and N1-1862 (also referred to as P503S) were examined in a variety of normal and tumor tissues using RT-PCR.

Briefly, total RNA was extracted from a variety of normal and tumor  
10 tissues using Trizol reagent as described above. First strand synthesis was carried out using 1-2  $\mu$ g of total RNA with SuperScript II reverse transcriptase (BRL Life Technologies) at 42 °C for one hour. The cDNA was then amplified by PCR with gene-specific primers. To ensure the semi-quantitative nature of the RT-PCR,  $\beta$ -actin was used as an internal control for each of the tissues examined. First, serial dilutions of the  
15 first strand cDNAs were prepared and RT-PCR assays were performed using  $\beta$ -actin specific primers. A dilution was then chosen that enabled the linear range amplification of the  $\beta$ -actin template and which was sensitive enough to reflect the differences in the initial copy numbers. Using these conditions, the  $\beta$ -actin levels were determined for each reverse transcription reaction from each tissue. DNA contamination was  
20 minimized by DNase treatment and by assuring a negative PCR result when using first strand cDNA that was prepared without adding reverse transcriptase.

mRNA Expression levels were examined in four different types of tumor tissue (prostate tumor from 2 patients, breast tumor from 3 patients, colon tumor, lung tumor), and sixteen different normal tissues, including prostate, colon, kidney, liver,  
25 lung, ovary, pancreas, skeletal muscle, skin, stomach, testes, bone marrow and brain. F1-16 was found to be expressed at high levels in prostate tumor tissue, colon tumor and normal prostate, and at lower levels in normal liver, skin and testes, with expression being undetectable in the other tissues examined. H1-1 was found to be expressed at high levels in prostate tumor, lung tumor, breast tumor, normal prostate, normal colon  
30 and normal brain, at much lower levels in normal lung, pancreas, skeletal muscle, skin,

small intestine, bone marrow, and was not detected in the other tissues tested. J1-17 (P502S) and L1-12 (P501S) appear to be specifically over-expressed in prostate, with both genes being expressed at high levels in prostate tumor and normal prostate but at low to undetectable levels in all the other tissues examined. N1-1862 (P503S) was found to be over-expressed in 60% of prostate tumors and detectable in normal colon and kidney. The RT-PCR results thus indicate that F1-16, H1-1, J1-17 (P502S), N1-1862 (P503S) and L1-12 (P501S) are either prostate specific or are expressed at significantly elevated levels in prostate.

Further RT-PCR studies showed that F1-12 (P504S) is over-expressed in 60% of prostate tumors, detectable in normal kidney but not detectable in all other tissues tested. Similarly, R1-2330 was shown to be over-expressed in 40% of prostate tumors, detectable in normal kidney and liver, but not detectable in all other tissues tested. U1-3064 was found to be over-expressed in 60% of prostate tumors, and also expressed in breast and colon tumors, but was not detectable in normal tissues.

RT-PCR characterization of R1-2330, U1-3064 and 1D-4279 showed that these three antigens are over-expressed in prostate and/or prostate tumors.

Northern analysis with four prostate tumors, two normal prostate samples, two BPH prostates, and normal colon, kidney, liver, lung, pancreas, skeletal muscle, brain, stomach, testes, small intestine and bone marrow, showed that L1-12 (P501S) is over-expressed in prostate tumors and normal prostate, while being undetectable in other normal tissues tested. J1-17 (P502S) was detected in two prostate tumors and not in the other tissues tested. N1-1862 (P503S) was found to be over-expressed in three prostate tumors and to be expressed in normal prostate, colon and kidney, but not in other tissues tested. F1-12 (P504S) was found to be highly expressed in two prostate tumors and to be undetectable in all other tissues tested.

The microarray technology described above was used to determine the expression levels of representative antigens described herein in prostate tumor, breast tumor and the following normal tissues: prostate, liver, pancreas, skin, bone marrow, brain, breast, adrenal gland, bladder, testes, salivary gland, large intestine, kidney, ovary, lung, spinal cord, skeletal muscle and colon. L1-12 (P501S) was found to be



over-expressed in normal prostate and prostate tumor, with some expression being detected in normal skeletal muscle. Both J1-12 and F1-12 (P504S) were found to be over-expressed in prostate tumor, with expression being lower or undetectable in all other tissues tested. N1-1862 (P503S) was found to be expressed at high levels in prostate tumor and normal prostate, and at low levels in normal large intestine and normal colon, with expression being undetectable in all other tissues tested. R1-2330 was found to be over-expressed in prostate tumor and normal prostate, and to be expressed at lower levels in all other tissues tested. 1D-4279 was found to be over-expressed in prostate tumor and normal prostate, expressed at lower levels in normal spinal cord, and to be undetectable in all other tissues tested.

Further microarray analysis to specifically address the extent to which P501S (SEQ ID NO: 110) was expressed in breast tumor revealed moderate over-expression not only in breast tumor, but also in metastatic breast tumor (2/31), with negligible to low expression in normal tissues. This data suggests that P501S may be over-expressed in various breast tumors as well as in prostate tumors.

The expression levels of 32 ESTs (expressed sequence tags) described by Vasmatzis *et al.* (*Proc. Natl. Acad. Sci. USA* 95:300-304, 1998) in a variety of tumor and normal tissues were examined by microarray technology as described above. Two of these clones (referred to as P1000C and P1001C) were found to be over-expressed in prostate tumor and normal prostate, and expressed at low to undetectable levels in all other tissues tested (normal aorta, thymus, resting and activated PBMC, epithelial cells, spinal cord, adrenal gland, fetal tissues, skin, salivary gland, large intestine, bone marrow, liver, lung, dendritic cells, stomach, lymph nodes, brain, heart, small intestine, skeletal muscle, colon and kidney. The determined cDNA sequences for P1000C and P1001C are provided in SEQ ID NO: 384 and 472, respectively. The sequence of P1001C was found to show some homology to the previously isolated Human mRNA for JM27 protein. Subsequent comparison of the sequence of SEQ ID NO: 384 with sequences in the public databases, led to the identification of a full-length cDNA sequence of P1000C (SEQ ID NO: 786), which encodes a 492 amino acid sequence. Analysis of the amino acid sequence using the PSORT II program led to the

identification of a putative transmembrane domain from amino acids 84-100. The cDNA sequence of the open reading frame of P1000C, including the stop codon, is provided in SEQ ID NO: 787, with the open reading frame without the stop codon being provided in SEQ ID NO: 788. The full-length amino acid sequence of P1000C is  
5 provided in SEQ ID NO: 789. SEQ ID NO: 790 and 791 represent amino acids 1-100 and 100-492 of P1000C, respectively.

The expression of the polypeptide encoded by the full length cDNA sequence for F1-12 (also referred to as P504S; SEQ ID NO: 108) was investigated by immunohistochemical analysis. Rabbit-anti-P504S polyclonal antibodies were  
10 generated against the full length P504S protein by standard techniques. Subsequent isolation and characterization of the polyclonal antibodies were also performed by techniques well known in the art. Immunohistochemical analysis showed that the P504S polypeptide was expressed in 100% of prostate carcinoma samples tested (n=5).

The rabbit-anti-P504S polyclonal antibody did not appear to label benign  
15 prostate cells with the same cytoplasmic granular staining, but rather with light nuclear staining. Analysis of normal tissues revealed that the encoded polypeptide was found to be expressed in some, but not all normal human tissues. Positive cytoplasmic staining with rabbit-anti-P504S polyclonal antibody was found in normal human kidney, liver, brain, colon and lung-associated macrophages, whereas heart and bone marrow were  
20 negative.

This data indicates that the P504S polypeptide is present in prostate cancer tissues, and that there are qualitative and quantitative differences in the staining between benign prostatic hyperplasia tissues and prostate cancer tissues, suggesting that this polypeptide may be detected selectively in prostate tumors and therefore be useful  
25 in the diagnosis of prostate cancer.

## EXAMPLE 3

ISOLATION AND CHARACTERIZATION OF PROSTATE-SPECIFIC  
POLYPEPTIDES BY PCR-BASED SUBTRACTION

5 A cDNA subtraction library, containing cDNA from normal prostate subtracted with ten other normal tissue cDNAs (brain, heart, kidney, liver, lung, ovary, placenta, skeletal muscle, spleen and thymus) and then submitted to a first round of PCR amplification, was purchased from Clontech. This library was subjected to a second round of PCR amplification, following the manufacturer's protocol. The  
10 resulting cDNA fragments were subcloned into the vector pT7 Blue T-vector (Novagen, Madison, WI) and transformed into XL-1 Blue MRF' *E. coli* (Stratagene). DNA was isolated from independent clones and sequenced using a Perkin Elmer/Applied Biosystems Division Automated Sequencer Model 373A.

Fifty-nine positive clones were sequenced. Comparison of the DNA  
15 sequences of these clones with those in the gene bank, as described above, revealed no significant homologies to 25 of these clones, hereinafter referred to as P5, P8, P9, P18, P20, P30, P34, P36, P38, P39, P42, P49, P50, P53, P55, P60, P64, P65, P73, P75, P76, P79 and P84. The determined cDNA sequences for these clones are provided in SEQ ID NO: 41-45, 47-52 and 54-65, respectively. P29, P47, P68, P80 and P82 (SEQ ID  
20 NO: 46, 53 and 66-68, respectively) were found to show some degree of homology to previously identified DNA sequences. To the best of the inventors' knowledge, none of these sequences have been previously shown to be present in prostate.

Further studies employing the sequence of SEQ ID NO: 67 as a probe in standard full-length cloning methods, resulted in the isolation of three cDNA sequences  
25 which appear to be splice variants of P80 (also known as P704P). These sequences are provided in SEQ ID NO: 620-622.

Further studies using the PCR-based methodology described above resulted in the isolation of more than 180 additional clones, of which 23 clones were found to show no significant homologies to known sequences. The determined cDNA  
30 sequences for these clones are provided in SEQ ID NO: 115-123, 127, 131, 137, 145,

147-151, 153, 156-158 and 160. Twenty-three clones (SEQ ID NO: 124-126, 128-130, 132-136, 138-144, 146, 152, 154, 155 and 159) were found to show some homology to previously identified ESTs. An additional ten clones (SEQ ID NO: 161-170) were found to have some degree of homology to known genes. Larger cDNA clones  
5 containing the P20 sequence represent splice variants of a gene referred to as P703P. The determined DNA sequence for the variants referred to as DE1, DE13 and DE14 are provided in SEQ ID NOS: 171, 175 and 177, respectively, with the corresponding predicted amino acid sequences being provided in SEQ ID NO: 172, 176 and 178, respectively. The determined cDNA sequence for an extended spliced form of P703 is  
10 provided in SEQ ID NO: 225. The DNA sequences for the splice variants referred to as DE2 and DE6 are provided in SEQ ID NOS: 173 and 174, respectively.

mRNA Expression levels for representative clones in tumor tissues (prostate (n=5), breast (n=2), colon and lung) normal tissues (prostate (n=5), colon, kidney, liver, lung (n=2), ovary (n=2), skeletal muscle, skin, stomach, small intestine  
15 and brain), and activated and non-activated PBMC was determined by RT-PCR as described above. Expression was examined in one sample of each tissue type unless otherwise indicated.

P9 was found to be highly expressed in normal prostate and prostate tumor compared to all normal tissues tested except for normal colon which showed  
20 comparable expression. P20, a portion of the P703P gene, was found to be highly expressed in normal prostate and prostate tumor, compared to all twelve normal tissues tested. A modest increase in expression of P20 in breast tumor (n=2), colon tumor and lung tumor was seen compared to all normal tissues except lung (1 of 2). Increased expression of P18 was found in normal prostate, prostate tumor and breast tumor  
25 compared to other normal tissues except lung and stomach. A modest increase in expression of P5 was observed in normal prostate compared to most other normal tissues. However, some elevated expression was seen in normal lung and PBMC. Elevated expression of P5 was also observed in prostate tumors (2 of 5), breast tumor and one lung tumor sample. For P30, similar expression levels were seen in normal  
30 prostate and prostate tumor, compared to six of twelve other normal tissues tested.

Increased expression was seen in breast tumors, one lung tumor sample and one colon tumor sample, and also in normal PBMC. P29 was found to be over-expressed in prostate tumor (5 of 5) and normal prostate (5 of 5) compared to the majority of normal tissues. However, substantial expression of P29 was observed in normal colon and  
5 normal lung (2 of 2). P80 was found to be over-expressed in prostate tumor (5 of 5) and normal prostate (5 of 5) compared to all other normal tissues tested, with increased expression also being seen in colon tumor.

Further studies resulted in the isolation of twelve additional clones, hereinafter referred to as 10-d8, 10-h10, 11-c8, 7-g6, 8-b5, 8-b6, 8-d4, 8-d9, 8-g3, 8-  
10 h11, 9-f12 and 9-f3. The determined DNA sequences for 10-d8, 10-h10, 11-c8, 8-d4, 8-d9, 8-h11, 9-f12 and 9-f3 are provided in SEQ ID NO: 207, 208, 209, 216, 217, 220, 221 and 222, respectively. The determined forward and reverse DNA sequences for 7-g6, 8-b5, 8-b6 and 8-g3 are provided in SEQ ID NO: 210 and 211; 212 and 213; 214 and 215; and 218 and 219, respectively. Comparison of these sequences with those in  
15 the gene bank revealed no significant homologies to the sequence of 9-f3. The clones 10-d8, 11-c8 and 8-h11 were found to show some homology to previously isolated ESTs, while 10-h10, 8-b5, 8-b6, 8-d4, 8-d9, 8-g3 and 9-f12 were found to show some homology to previously identified genes. Further characterization of 7-G6 and 8-G3 showed identity to the known genes PAP and PSA, respectively.

20 mRNA expression levels for these clones were determined using the micro-array technology described above. The clones 7-G6, 8-G3, 8-B5, 8-B6, 8-D4, 8-D9, 9-F3, 9-F12, 9-H3, 10-A2, 10-A4, 11-C9 and 11-F2 were found to be over-expressed in prostate tumor and normal prostate, with expression in other tissues tested being low or undetectable. Increased expression of 8-F11 was seen in prostate tumor  
25 and normal prostate, bladder, skeletal muscle and colon. Increased expression of 10-H10 was seen in prostate tumor and normal prostate, bladder, lung, colon, brain and large intestine. Increased expression of 9-B1 was seen in prostate tumor, breast tumor, and normal prostate, salivary gland, large intestine and skin, with increased expression of 11-C8 being seen in prostate tumor, and normal prostate and large intestine.

An additional cDNA fragment derived from the PCR-based normal prostate subtraction, described above, was found to be prostate specific by both microarray technology and RT-PCR. The determined cDNA sequence of this clone (referred to as 9-A11) is provided in SEQ ID NO: 226. Comparison of this sequence with those  
5 in the public databases revealed 99% identity to the known gene HOXB13.

Further studies led to the isolation of the clones 8-C6 and 8-H7. The determined cDNA sequences for these clones are provided in SEQ ID NO: 227 and 228, respectively. These sequences were found to show some homology to previously isolated ESTs.

10 PCR and hybridization-based methodologies were employed to obtain longer cDNA sequences for clone P20 (also referred to as P703P), yielding three additional cDNA fragments that progressively extend the 5' end of the gene. These fragments, referred to as P703PDE5, P703P6.26, and P703PX-23 (SEQ ID NO: 326, 328 and 330, with the predicted corresponding amino acid sequences being provided in  
15 SEQ ID NO: 327, 329 and 331, respectively) contain additional 5' sequence. P703PDE5 was recovered by screening of a cDNA library (#141-26) with a portion of P703P as a probe. P703P6.26 was recovered from a mixture of three prostate tumor cDNAs and P703PX\_23 was recovered from cDNA library (#438-48). Together, the additional sequences include all of the putative mature serine protease along with part of  
20 the putative signal sequence. The full-length cDNA sequence for P703P is provided in SEQ ID NO: 524, with the corresponding amino acid sequence being provided in SEQ ID NO: 525.

Using computer algorithms, the following regions of P703P were predicted to represent potential HLA A2-binding CTL epitopes: amino acids 164-172  
25 of SEQ ID NO: 525 (SEQ ID NO: 723); amino acids 160-168 of SEQ ID NO: 525 (SEQ ID NO: 724); amino acids 239-247 of SEQ ID NO: 525 (SEQ ID NO: 725); amino acids 118-126 of SEQ ID NO: 525 (SEQ ID NO: 726); amino acids 112-120 of SEQ ID NO: 525 (SEQ ID NO: 727); amino acids 155-164 of SEQ ID NO: 525 (SEQ ID NO: 728); amino acids 117-126 of SEQ ID NO: 525 (SEQ ID NO: 729); amino acids  
30 164-173 of SEQ ID NO: 525 (SEQ ID NO: 730); amino acids 154-163 of SEQ ID NO:

525 (SEQ ID NO: 731); amino acids 163-172 of SEQ ID NO: 525 (SEQ ID NO: 732); amino acids 58-66 of SEQ ID NO: 525 (SEQ ID NO: 733); and amino acids 59-67 of SEQ ID NO: 525 (SEQ ID NO: 734).

P703P was found to show some homology to previously identified  
5 proteases, such as thrombin. The thrombin receptor has been shown to be preferentially expressed in highly metastatic breast carcinoma cells and breast carcinoma biopsy samples. Introduction of thrombin receptor antisense cDNA has been shown to inhibit the invasion of metastatic breast carcinoma cells in culture. Antibodies against thrombin receptor inhibit thrombin receptor activation and thrombin-induced platelet  
10 activation. Furthermore, peptides that resemble the receptor's tethered ligand domain inhibit platelet aggregation by thrombin. P703P may play a role in prostate cancer through a protease-activated receptor on the cancer cell or on stromal cells. The potential trypsin-like protease activity of P703P may either activate a protease-activated receptor on the cancer cell membrane to promote tumorigenesis or activate a protease-  
15 activated receptor on the adjacent cells (such as stromal cells) to secrete growth factors and/or proteases (such as matrix metalloproteinases) that could promote tumor angiogenesis, invasion and metastasis. P703P may thus promote tumor progression and/or metastasis through the activation of protease-activated receptor. Polypeptides and antibodies that block the P703P-receptor interaction may therefore be usefully  
20 employed in the treatment of prostate cancer.

To determine whether P703P expression increases with increased severity of Gleason grade, an indicator of tumor stage, quantitative PCR analysis was performed on prostate tumor samples with a range of Gleason scores from 5 to > 8. The mean level of P703P expression increased with increasing Gleason score, indicating that  
25 P703P expression may correlate with increased disease severity.

Further studies using a PCR-based subtraction library of a prostate tumor pool subtracted against a pool of normal tissues (referred to as JP: PCR subtraction) resulted in the isolation of thirteen additional clones, seven of which did not share any significant homology to known GenBank sequences. The determined cDNA sequences  
30 for these seven clones (P711P, P712P, novel 23, P774P, P775P, P710P and P768P) are

provided in SEQ ID NO: 307-311, 313 and 315, respectively. The remaining six clones (SEQ ID NO: 316 and 321-325) were shown to share some homology to known genes. By microarray analysis, all thirteen clones showed three or more fold over-expression in prostate tissues, including prostate tumors, BPH and normal prostate as compared to normal non-prostate tissues. Clones P711P, P712P, novel 23 and P768P showed over-expression in most prostate tumors and BPH tissues tested (n=29), and in the majority of normal prostate tissues (n=4), but background to low expression levels in all normal tissues. Clones P774P, P775P and P710P showed comparatively lower expression and expression in fewer prostate tumors and BPH samples, with negative to low expression in normal prostate.

Further studies led to the isolation of an extended cDNA sequence for P712P (SEQ ID NO: 552). The amino acid sequences encoded by 16 predicted open reading frames present within the sequence of SEQ ID NO: 552 are provided in SEQ ID NO: 553-568.

The full-length cDNA for P711P was obtained by employing the partial sequence of SEQ ID NO: 307 to screen a prostate cDNA library. Specifically, a directionally cloned prostate cDNA library was prepared using standard techniques. One million colonies of this library were plated onto LB/Amp plates. Nylon membrane filters were used to lift these colonies, and the cDNAs which were picked up by these filters were denatured and cross-linked to the filters by UV light. The P711P cDNA fragment of SEQ ID NO: 307 was radio-labeled and used to hybridize with these filters. Positive clones were selected, and cDNAs were prepared and sequenced using an automatic Perkin Elmer/Applied Biosystems sequencer. The determined full-length sequence of P711P is provided in SEQ ID NO: 382, with the corresponding predicted amino acid sequence being provided in SEQ ID NO: 383.

Using PCR and hybridization-based methodologies, additional cDNA sequence information was derived for two clones described above, 11-C9 and 9-F3, herein after referred to as P707P and P714P, respectively (SEQ ID NO: 333 and 334). After comparison with the most recent GenBank, P707P was found to be a splice variant of the known gene HoxB13. In contrast, no significant homologies to P714P



were found. Further studies employing the sequence of SEQ ID NO: 334 as a probe in standard full-length cloning methods, resulted in an extended cDNA sequence for P714P. This sequence is provided in SEQ ID NO: 619. This sequence was found to show some homology to the gene that encodes human ribosomal L23A protein.

5 Clones 8-B3, P89, P98, P130 and P201 (as disclosed in U.S. Patent Application No. 09/020,956, filed February 9, 1998) were found to be contained within one contiguous sequence, referred to as P705P (SEQ ID NO: 335, with the predicted amino acid sequence provided in SEQ ID NO: 336), which was determined to be a splice variant of the known gene NKX 3.1.

10 Further studies on P775P resulted in the isolation of four additional sequences (SEQ ID NO: 473-476) which are all splice variants of the P775P gene. The sequence of SEQ ID NO: 474 was found to contain two open reading frames (ORFs). The predicted amino acid sequences encoded by these ORFs are provided in SEQ ID NO: 477 and 478. The cDNA sequence of SEQ ID NO: 475 was found to contain an  
15 ORF which encodes the amino acid sequence of SEQ ID NO: 479. The cDNA sequence of SEQ ID NO: 473 was found to contain four ORFs. The predicted amino acid sequences encoded by these ORFs are provided in SEQ ID NO: 480-483. Additional splice variants of P775P are provided in SEQ ID NO: 593-597.

Subsequent studies led to the identification of a genomic region on  
20 chromosome 22q11.2, known as the Cat Eye Syndrome region, that contains the five prostate genes P704P, P712P, P774P, P775P and B305D. The relative location of each of these five genes within the genomic region is shown in Fig. 10. This region may therefore be associated with malignant tumors, and other potential tumor genes may be contained within this region. These studies also led to the identification of a potential  
25 open reading frame (ORF) for P775P (provided in SEQ ID NO: 533), which encodes the amino acid sequence of SEQ ID NO: 534.

Comparison of the clone of SEQ ID NO: 325 (referred to as P558S) with sequences in the GenBank and GeneSeq DNA databases showed that P558S is identical to the prostate-specific transglutaminase gene, which is known to have two forms. The  
30 full-length sequences for the two forms are provided in SEQ ID NO: 630 and 631, with

the corresponding amino acid sequences being provided in SEQ ID NO: 632 and 633, respectively. The cDNA sequence of SEQ ID NO: 631 has a 15 pair base insert, resulting in a 5 amino acid insert in the corresponding amino acid sequence (SEQ ID NO: 633). This insert is not present in the sequence of SEQ ID NO: 630.

5 Further studies on P768P (SEQ ID NO: 315) led to the identification of the putative full-length open reading frame (ORF). The cDNA sequence of the ORF with stop codon is provided in SEQ ID NO: 764. The cDNA sequence of the ORF without stop codon is provided in SEQ ID NO: 765, with the corresponding amino acid sequence being provided in SEQ ID NO: 766. This sequence was found to show 86%  
10 identity to a rat calcium transporter protein, indicating that P768P may represent a human calcium transporter protein. The locations of transmembrane domains within P768P were predicted using the PSORT II computer algorithm. Six transmembrane domains were predicted at amino acid positions 118-134, 172-188, 211-227, 230-246, 282-298 and 348-364. The amino acid sequences of SEQ ID NO: 767-772 represent  
15 amino acids 1-134, 135-188, 189-227, 228-246, 247-298 and 299-511 of P768P, respectively.

#### EXAMPLE 4

##### SYNTHESIS OF POLYPEPTIDES

20 Polypeptides may be synthesized on a Perkin Elmer/Applied Biosystems 430A peptide synthesizer using Fmoc chemistry with HPTU (O-Benzotriazole-N,N,N',N'-tetramethyluronium hexafluorophosphate) activation. A Gly-Cys-Gly sequence may be attached to the amino terminus of the peptide to provide a method of  
25 conjugation, binding to an immobilized surface, or labeling of the peptide. Cleavage of the peptides from the solid support may be carried out using the following cleavage mixture: trifluoroacetic acid:ethanedithiol:thioanisole:water:phenol (40:1:2:2:3). After cleaving for 2 hours, the peptides may be precipitated in cold methyl-t-butyl-ether. The peptide pellets may then be dissolved in water containing 0.1% trifluoroacetic acid  
30 (TFA) and lyophilized prior to purification by C18 reverse phase HPLC. A gradient of

0%-60% acetonitrile (containing 0.1% TFA) in water (containing 0.1% TFA) may be used to elute the peptides. Following lyophilization of the pure fractions, the peptides may be characterized using electrospray or other types of mass spectrometry and by amino acid analysis.

5

## EXAMPLE 5

### FURTHER ISOLATION AND CHARACTERIZATION OF PROSTATE-SPECIFIC POLYPEPTIDES BY PCR-BASED SUBTRACTION

10 A cDNA library generated from prostate primary tumor mRNA as described above was subtracted with cDNA from normal prostate. The subtraction was performed using a PCR-based protocol (Clontech), which was modified to generate larger fragments. Within this protocol, tester and driver double stranded cDNA were separately digested with five restriction enzymes that recognize six-nucleotide  
15 restriction sites (MluI, MscI, PvuII, SalI and StuI). This digestion resulted in an average cDNA size of 600 bp, rather than the average size of 300 bp that results from digestion with RsaI according to the Clontech protocol. This modification did not affect the subtraction efficiency. Two tester populations were then created with different adapters, and the driver library remained without adapters.

20 The tester and driver libraries were then hybridized using excess driver cDNA. In the first hybridization step, driver was separately hybridized with each of the two tester cDNA populations. This resulted in populations of (a) unhybridized tester cDNAs, (b) tester cDNAs hybridized to other tester cDNAs, (c) tester cDNAs hybridized to driver cDNAs and (d) unhybridized driver cDNAs. The two separate  
25 hybridization reactions were then combined, and rehybridized in the presence of additional denatured driver cDNA. Following this second hybridization, in addition to populations (a) through (d), a fifth population (e) was generated in which tester cDNA with one adapter hybridized to tester cDNA with the second adapter. Accordingly, the second hybridization step resulted in enrichment of differentially expressed sequences  
30 which could be used as templates for PCR amplification with adaptor-specific primers.

The ends were then filled in, and PCR amplification was performed using adaptor-specific primers. Only population (e), which contained tester cDNA that did not hybridize to driver cDNA, was amplified exponentially. A second PCR amplification step was then performed, to reduce background and further enrich  
5 differentially expressed sequences.

This PCR-based subtraction technique normalizes differentially expressed cDNAs so that rare transcripts that are overexpressed in prostate tumor tissue may be recoverable. Such transcripts would be difficult to recover by traditional subtraction methods.

10 In addition to genes known to be overexpressed in prostate tumor, seventy-seven further clones were identified. Sequences of these partial cDNAs are provided in SEQ ID NO: 29 to 305. Most of these clones had no significant homology to database sequences. Exceptions were JPTPN23 (SEQ ID NO: 231; similarity to pig valosin-containing protein), JPTPN30 (SEQ ID NO: 234; similarity to rat mRNA for  
15 proteasome subunit), JPTPN45 (SEQ ID NO: 243; similarity to rat *norvegicus* cytosolic NADP-dependent isocitrate dehydrogenase), JPTPN46 (SEQ ID NO: 244; similarity to human subclone H8 4 d4 DNA sequence), JP1D6 (SEQ ID NO: 265; similarity to *G. gallus* dynein light chain-A), JP8D6 (SEQ ID NO: 288; similarity to human BAC clone RG016J04), JP8F5 (SEQ ID NO: 289; similarity to human subclone H8 3 b5 DNA  
20 sequence), and JP8E9 (SEQ ID NO: 299; similarity to human Alu sequence).

Additional studies using the PCR-based subtraction library consisting of a prostate tumor pool subtracted against a normal prostate pool (referred to as PT-PN PCR subtraction) yielded three additional clones. Comparison of the cDNA sequences of these clones with the most recent release of GenBank revealed no significant  
25 homologies to the two clones referred to as P715P and P767P (SEQ ID NO: 312 and 314). The remaining clone was found to show some homology to the known gene KIAA0056 (SEQ ID NO: 318). Using microarray analysis to measure mRNA expression levels in various tissues, all three clones were found to be over-expressed in prostate tumors and BPH tissues. Specifically, clone P715P was over-expressed in most  
30 prostate tumors and BPH tissues by a factor of three or greater, with elevated expression

seen in the majority of normal prostate samples and in fetal tissue, but negative to low expression in all other normal tissues. Clone P767P was over-expressed in several prostate tumors and BPH tissues, with moderate expression levels in half of the normal prostate samples, and background to low expression in all other normal tissues tested.

5 Further analysis, by microarray as described above, of the PT-PN PCR subtraction library and of a DNA subtraction library containing cDNA from prostate tumor subtracted with a pool of normal tissue cDNAs, led to the isolation of 27 additional clones (SEQ ID NO: 340-365 and 381) which were determined to be over-expressed in prostate tumor. The clones of SEQ ID NO: 341, 342, 345, 347, 348, 349,  
10 351, 355-359, 361, 362 and 364 were also found to be expressed in normal prostate. Expression of all 26 clones in a variety of normal tissues was found to be low or undetectable, with the exception of P544S (SEQ ID NO: 356) which was found to be expressed in small intestine. Of the 26 clones, 11 (SEQ ID NO: 340-349 and 362) were found to show some homology to previously identified sequences. No significant  
15 homologies were found to the clones of SEQ ID NO: 350, 351, 353-361, and 363-365.

Comparison of the sequence of SEQ ID NO: 362 with sequences in the GenBank and GeneSeq DNA databases showed that this clone (referred to as P788P) is identical to GeneSeq Accession No. X27262, which encodes a protein found in the GeneSeq protein Accession No. Y00931. The full length cDNA sequence of P788P is  
20 provided in SEQ ID NO: 634, with the corresponding predicted amino acid being provided in SEQ ID NO: 635. Subsequently, a full-length cDNA sequence for P788P that contains polymorphisms not found in the sequence of SEQ ID NO: 634, was cloned multiple times by PCR amplification from cDNA prepared from several RNA templates from three individuals. This determined cDNA sequence of this polymorphic variant of  
25 P788P is provided in SEQ ID NO: 636, with the corresponding amino acid sequence being provided in SEQ ID NO: 637. The sequence of SEQ ID NO: 637 differs from that of SEQ ID NO: 635 by six amino acid residues. The P788P protein has 7 potential transmembrane domains at the C-terminal portion and is predicted to be a plasma membrane protein with an extracellular N-terminal region.

Further studies on the clone of SEQ ID NO: 352 (referred to as P790P) led to the isolation of the full-length cDNA sequence of SEQ ID NO: 526. The corresponding predicted amino acid is provided in SEQ ID NO: 527. Data from two quantitative PCR experiments indicated that P790P is over-expressed in 11/15 tested prostate tumor samples and is expressed at low levels in spinal cord, with no expression being seen in all other normal samples tested. Data from further PCR experiments and microarray experiments showed over-expression in normal prostate and prostate tumor with little or no expression in other tissues tested. P790P was subsequently found to show significant homology to a previously identified G-protein coupled prostate tissue receptor.

Additional studies on the clone of SEQ ID NO: 354 (referred to as P776P) led to the isolation of an extended cDNA sequence, provided in SEQ ID NO: 569. The determined cDNA sequences of three additional splice variants of P776P are provided in SEQ ID NO: 570-572. The amino acid sequences encoded by two predicted open reading frames (ORFs) contained within SEQ ID NO: 570, one predicted ORF contained within SEQ ID NO: 571, and 11 predicted ORFs contained within SEQ ID NO: 569, are provided in SEQ ID NO: 573-586, respectively. Further studies led to the isolation of the full-length sequence for the clone of SEQ ID NO: 570 (provided in SEQ ID NO: 737). Full-length cloning efforts on the clone of SEQ ID NO: 571 led to the isolation of two sequences (provided in SEQ ID NO: 738 and 739), representing a single clone, that are identical with the exception of a polymorphic insertion/deletion at position 1293. Specifically, the clone of SEQ ID NO: 739 (referred to as clone F1) has a C at position 1293. The clone of SEQ ID NO: 738 (referred to as clone F2) has a single base pair deletion at position 1293. The predicted amino acid sequences encoded by 5 open reading frames located within SEQ ID NO: 737 are provided in SEQ ID NO: 740-744, with the predicted amino acid sequences encoded by the clone of SEQ ID NO: 738 and 739 being provided in SEQ ID NO: 745-750.

Comparison of the cDNA sequences for the clones P767P (SEQ ID NO: 314) and P777P (SEQ ID NO: 350) with sequences in the GenBank human EST database showed that the two clones matched many EST sequences in common,

suggesting that P767P and P777P may represent the same gene. A DNA consensus sequence derived from a DNA sequence alignment of P767P, P777P and multiple EST clones is provided in SEQ ID NO: 587. The amino acid sequences encoded by three putative ORFs located within SEQ ID NO: 587 are provided in SEQ ID NO: 588-590.

- 5           The clone of SEQ ID NO: 342 (referred to as P789P) was found to show homology to a previously identified gene. The full length cDNA sequence for P789P and the corresponding amino acid sequence are provided in SEQ ID NO: 735 and 736, respectively.

10

## EXAMPLE 6

### PEPTIDE PRIMING OF MICE AND PROPAGATION OF CTL LINES

6.1. This Example illustrates the preparation of a CTL cell line specific for cells expressing the P502S gene.

- 15           Mice expressing the transgene for human HLA A2Kb (provided by Dr L. Sherman, The Scripps Research Institute, La Jolla, CA) were immunized with P2S#12 peptide (VLGWVAEL; SEQ ID NO: 306), which is derived from the P502S gene (also referred to herein as J1-17, SEQ ID NO: 8), as described by Theobald et al., *Proc. Natl. Acad. Sci. USA* 92:11993-11997, 1995 with the following modifications. Mice were  
20 immunized with 100µg of P2S#12 and 120µg of an I-A<sup>b</sup> binding peptide derived from hepatitis B Virus protein emulsified in incomplete Freund's adjuvant. Three weeks later these mice were sacrificed and using a nylon mesh single cell suspensions prepared. Cells were then resuspended at  $6 \times 10^6$  cells/ml in complete media (RPMI-1640; Gibco BRL, Gaithersburg, MD) containing 10% FCS, 2mM Glutamine (Gibco BRL), sodium  
25 pyruvate (Gibco BRL), non-essential amino acids (Gibco BRL),  $2 \times 10^{-5}$  M 2-mercaptoethanol, 50U/ml penicillin and streptomycin, and cultured in the presence of irradiated (3000 rads) P2S#12-pulsed (5mg/ml P2S#12 and 10mg/ml  $\beta$ 2-microglobulin) LPS blasts (A2 transgenic spleens cells cultured in the presence of 7µg/ml dextran sulfate and 25µg/ml LPS for 3 days). Six days later, cells ( $5 \times 10^5$ /ml) were  
30 restimulated with  $2.5 \times 10^6$ /ml peptide pulsed irradiated (20,000 rads) EL4A2Kb cells

(Sherman et al, *Science* 258:815-818, 1992) and  $3 \times 10^6$ /ml A2 transgenic spleen feeder cells. Cells were cultured in the presence of 20U/ml IL-2. Cells continued to be restimulated on a weekly basis as described, in preparation for cloning the line.

P2S#12 line was cloned by limiting dilution analysis with peptide pulsed  
5 EL4 A2Kb tumor cells ( $1 \times 10^4$  cells/ well) as stimulators and A2 transgenic spleen cells as feeders ( $5 \times 10^5$  cells/ well) grown in the presence of 30U/ml IL-2. On day 14, cells were restimulated as before. On day 21, clones that were growing were isolated and maintained in culture. Several of these clones demonstrated significantly higher reactivity (lysis) against human fibroblasts (HLA A2Kb expressing) transduced with  
10 P502S than against control fibroblasts. An example is presented in Figure 1.

This data indicates that P2S #12 represents a naturally processed epitope of the P502S protein that is expressed in the context of the human HLA A2Kb molecule.

15 6.2. This Example illustrates the preparation of murine CTL lines and CTL clones specific for cells expressing the P501S gene.

This series of experiments were performed similarly to that described above. Mice were immunized with the P1S#10 peptide (SEQ ID NO: 337), which is  
20 derived from the P501S gene (also referred to herein as L1-12, SEQ ID NO: 110). The P1S#10 peptide was derived by analysis of the predicted polypeptide sequence for P501S for potential HLA-A2 binding sequences as defined by published HLA-A2 binding motifs (Parker, KC, et al, *J. Immunol.*, 152:163, 1994). P1S#10 peptide was synthesized as described in Example 4, and empirically tested for HLA-A2 binding  
25 using a T cell based competition assay. Predicted A2 binding peptides were tested for their ability to compete HLA-A2 specific peptide presentation to an HLA-A2 restricted CTL clone (D150M58), which is specific for the HLA-A2 binding influenza matrix peptide fluM58. D150M58 CTL secretes TNF in response to self-presentation of peptide fluM58. In the competition assay, test peptides at 100-200  $\mu$ g/ml were added to  
30 cultures of D150M58 CTL in order to bind HLA-A2 on the CTL. After thirty minutes,



CTL cultured with test peptides, or control peptides, were tested for their antigen dose response to the fluM58 peptide in a standard TNF bioassay. As shown in Figure 3, peptide P1S#10 competes HLA-A2 restricted presentation of fluM58, demonstrating that peptide P1S#10 binds HLA-A2.

5 Mice expressing the transgene for human HLA A2Kb were immunized as described by Theobald et al. (*Proc. Natl. Acad. Sci. USA* 92:11993-11997, 1995) with the following modifications. Mice were immunized with 62.5µg of P1S #10 and 120µg of an I-A<sup>b</sup> binding peptide derived from Hepatitis B Virus protein emulsified in incomplete Freund's adjuvant. Three weeks later these mice were sacrificed and single  
10 cell suspensions prepared using a nylon mesh. Cells were then resuspended at  $6 \times 10^6$  cells/ml in complete media (as described above) and cultured in the presence of irradiated (3000 rads) P1S#10-pulsed (2µg/ml P1S#10 and 10mg/ml β2-microglobulin) LPS blasts (A2 transgenic spleens cells cultured in the presence of 7µg/ml dextran sulfate and 25µg/ml LPS for 3 days). Six days later cells ( $5 \times 10^5$ /ml) were restimulated  
15 with  $2.5 \times 10^6$ /ml peptide-pulsed irradiated (20,000 rads) EL4A2Kb cells, as described above, and  $3 \times 10^6$ /ml A2 transgenic spleen feeder cells. Cells were cultured in the presence of 20 U/ml IL-2. Cells were restimulated on a weekly basis in preparation for cloning. After three rounds of *in vitro* stimulations, one line was generated that recognized P1S#10-pulsed Jurkat A2Kb targets and P501S-transduced Jurkat targets as  
20 shown in Figure 4.

A P1S#10-specific CTL line was cloned by limiting dilution analysis with peptide pulsed EL4 A2Kb tumor cells ( $1 \times 10^4$  cells/ well) as stimulators and A2 transgenic spleen cells as feeders ( $5 \times 10^5$  cells/ well) grown in the presence of 30U/ml IL-2. On day 14, cells were restimulated as before. On day 21, viable clones were  
25 isolated and maintained in culture. As shown in Figure 5, five of these clones demonstrated specific cytolytic reactivity against P501S-transduced Jurkat A2Kb targets. This data indicates that P1S#10 represents a naturally processed epitope of the P501S protein that is expressed in the context of the human HLA-A2.1 molecule.

## EXAMPLE 7

PRIMING OF CTL *IN VIVO* USING NAKED DNA IMMUNIZATION

## WITH A PROSTATE ANTIGEN

The prostate-specific antigen L1-12, as described above, is also referred  
5 to as P501S. HLA A2Kb Tg mice (provided by Dr L. Sherman, The Scripps Research  
Institute, La Jolla, CA) were immunized with 100 µg P501S in the vector VR1012  
either intramuscularly or intradermally. The mice were immunized three times, with a  
two week interval between immunizations. Two weeks after the last immunization,  
immune spleen cells were cultured with Jurkat A2Kb-P501S transduced stimulator  
10 cells. CTL lines were stimulated weekly. After two weeks of *in vitro* stimulation, CTL  
activity was assessed against P501S transduced targets. Two out of 8 mice developed  
strong anti-P501S CTL responses. These results demonstrate that P501S contains at  
least one naturally processed HLA-A2-restricted CTL epitope.

15

## EXAMPLE 8

## ABILITY OF HUMAN T CELLS TO RECOGNIZE PROSTATE-SPECIFIC POLYPEPTIDES

This Example illustrates the ability of T cells specific for a prostate  
tumor polypeptide to recognize human tumor.

20 Human CD8<sup>+</sup> T cells were primed *in vitro* to the P2S-12 peptide (SEQ  
ID NO: 306) derived from P502S (also referred to as J1-17) using dendritic cells  
according to the protocol of Van Tsai et al. (*Critical Reviews in Immunology* 18:65-75,  
1998). The resulting CD8<sup>+</sup> T cell microcultures were tested for their ability to  
recognize the P2S-12 peptide presented by autologous fibroblasts or fibroblasts which  
25 were transduced to express the P502S gene in a  $\gamma$ -interferon ELISPOT assay (*see*  
Lalvani et al., *J. Exp. Med.* 186:859-865, 1997). Briefly, titrating numbers of T cells  
were assayed in duplicate on 10<sup>4</sup> fibroblasts in the presence of 3 µg/ml human  $\beta_2$ -  
microglobulin and 1 µg/ml P2S-12 peptide or control E75 peptide. In addition, T cells  
were simultaneously assayed on autologous fibroblasts transduced with the P502S gene  
30 or as a control, fibroblasts transduced with HER-2/*neu*. Prior to the assay, the

fibroblasts were treated with 10 ng/ml  $\gamma$ -interferon for 48 hours to upregulate class I MHC expression. One of the microcultures (#5) demonstrated strong recognition of both peptide pulsed fibroblasts as well as transduced fibroblasts in a  $\gamma$ -interferon ELISPOT assay. Figure 2A demonstrates that there was a strong increase in the number of  $\gamma$ -interferon spots with increasing numbers of T cells on fibroblasts pulsed with the P2S-12 peptide (solid bars) but not with the control E75 peptide (open bars). This shows the ability of these T cells to specifically recognize the P2S-12 peptide. As shown in Figure 2B, this microculture also demonstrated an increase in the number of  $\gamma$ -interferon spots with increasing numbers of T cells on fibroblasts transduced to express the P502S gene but not the HER-2/*neu* gene. These results provide additional confirmatory evidence that the P2S-12 peptide is a naturally processed epitope of the P502S protein. Furthermore, this also demonstrates that there exists in the human T cell repertoire, high affinity T cells which are capable of recognizing this epitope. These T cells should also be capable of recognizing human tumors which express the P502S gene.

### EXAMPLE 9

#### ELICITATION OF PROSTATE ANTIGEN-SPECIFIC CTL RESPONSES IN HUMAN BLOOD

20

This Example illustrates the ability of a prostate-specific antigen to elicit a CTL response in blood of normal humans.

Autologous dendritic cells (DC) were differentiated from monocyte cultures derived from PBMC of normal donors by growth for five days in RPMI medium containing 10% human serum, 50 ng/ml GMCSF and 30 ng/ml IL-4. Following culture, DC were infected overnight with recombinant P501S-expressing vaccinia virus at an M.O.I. of 5 and matured for 8 hours by the addition of 2 micrograms/ml CD40 ligand. Virus was inactivated by UV irradiation, CD8<sup>+</sup> cells were isolated by positive selection using magnetic beads, and priming cultures were initiated in 24-well plates. Following five stimulation cycles using autologous fibroblasts

retrovirally transduced to express P501S and CD80, CD8<sup>+</sup> lines were identified that specifically produced interferon-gamma when stimulated with autologous P501S-transduced fibroblasts. The P501S-specific activity of cell line 3A-1 could be maintained following additional stimulation cycles on autologous B-LCL transduced with P501S. Line 3A-1 was shown to specifically recognize autologous B-LCL transduced to express P501S, but not EGFP-transduced autologous B-LCL, as measured by cytotoxicity assays (<sup>51</sup>Cr release) and interferon-gamma production (Interferon-gamma Elispot; *see above and Lalvani et al., J. Exp. Med. 186:859-865, 1997*). The results of these assays are presented in Figures 6A and 6B.

10

## EXAMPLE 10

IDENTIFICATION OF A NATURALLY PROCESSED CTL EPITOPE CONTAINED WITHIN THE  
PROSTATE-SPECIFIC ANTIGEN P703P

The 9-mer peptide p5 (SEQ ID NO: 338) was derived from the P703P antigen (also referred to as P20). The p5 peptide is immunogenic in human HLA-A2 donors and is a naturally processed epitope. Antigen specific human CD8<sup>+</sup> T cells can be primed following repeated *in vitro* stimulations with monocytes pulsed with p5 peptide. These CTL specifically recognize p5-pulsed and P703P-transduced target cells in both ELISPOT (as described above) and chromium release assays. Additionally, immunization of HLA-A2Kb transgenic mice with p5 leads to the generation of CTL lines which recognize a variety of HLA-A2Kb or HLA-A2 transduced target cells expressing P703P.

Initial studies demonstrating that p5 is a naturally processed epitope were done using HLA-A2Kb transgenic mice. HLA-A2Kb transgenic mice were immunized subcutaneously in the footpad with 100 µg of p5 peptide together with 140 µg of hepatitis B virus core peptide (a Th peptide) in Freund's incomplete adjuvant. Three weeks post immunization, spleen cells from immunized mice were stimulated *in vitro* with peptide-pulsed LPS blasts. CTL activity was assessed by chromium release assay five days after primary *in vitro* stimulation. Retrovirally transduced cells expressing the

30

control antigen P703P and HLA-A2Kb were used as targets. CTL lines that specifically recognized both p5-pulsed targets as well as P703P-expressing targets were identified.

Human *in vitro* priming experiments demonstrated that the p5 peptide is immunogenic in humans. Dendritic cells (DC) were differentiated from monocyte  
5 cultures derived from PBMC of normal human donors by culturing for five days in RPMI medium containing 10% human serum, 50 ng/ml human GM-CSF and 30 ng/ml human IL-4. Following culture, the DC were pulsed with 1 ug/ml p5 peptide and cultured with CD8<sup>+</sup> T cell enriched PBMC. CTL lines were restimulated on a weekly basis with p5-pulsed monocytes. Five to six weeks after initiation of the CTL cultures,  
10 CTL recognition of p5-pulsed target cells was demonstrated. CTL were additionally shown to recognize human cells transduced to express P703P, demonstrating that p5 is a naturally processed epitope.

Studies identifying a further peptide epitope (referred to as peptide 4) derived from the prostate tumor-specific antigen P703P that is capable of being  
15 recognized by CD4 T cells on the surface of cells in the context of HLA class II molecules were carried out as follows. The amino acid sequence for peptide 4 is provided in SEQ ID NO: 638, with the corresponding cDNA sequence being provided in SEQ ID NO: 639.

Twenty 15-mer peptides overlapping by 10 amino acids and derived  
20 from the carboxy-terminal fragment of P703P were generated using standard procedures. Dendritic cells (DC) were derived from PBMC of a normal female donor using GM-CSF and IL-4 by standard protocols. CD4 T cells were generated from the same donor as the DC using MACS beads and negative selection. DC were pulsed overnight with pools of the 15-mer peptides, with each peptide at a final concentration  
25 of 0.25 microgram/ml. Pulsed DC were washed and plated at  $1 \times 10^4$  cells/well of 96-well V-bottom plates and purified CD4 T cells were added at  $1 \times 10^5$ /well. Cultures were supplemented with 60 ng/ml IL-6 and 10 ng/ml IL-12 and incubated at 37 °C. Cultures were restimulated as above on a weekly basis using DC generated and pulsed as above as antigen presenting cells, supplemented with 5 ng/ml IL-7 and 10 u/ml IL-2.  
30 Following 4 *in vitro* stimulation cycles, 96 lines (each line corresponding to one well) were tested for specific proliferation and cytokine production in response to the

stimulating pools with an irrelevant pool of peptides derived from mammaglobin being used as a control.

One line (referred to as 1-F9) was identified from pool #1 that demonstrated specific proliferation (measured by <sup>3</sup>H proliferation assays) and cytokine production (measured by interferon-gamma ELISA assays) in response to pool #1 of P703P peptides. This line was further tested for specific recognition of the peptide pool, specific recognition of individual peptides in the pool, and in HLA mismatch analyses to identify the relevant restricting allele. Line 1-F9 was found to specifically proliferate and produce interferon-gamma in response to peptide pool #1, and also to peptide 4 (SEQ ID NO: 638). Peptide 4 corresponds to amino acids 126-140 of SEQ ID NO: 327. Peptide titration experiments were conducted to assess the sensitivity of line 1-F9 for the specific peptide. The line was found to specifically respond to peptide 4 at concentrations as low as 0.25 ng/ml, indicating that the T cells are very sensitive and therefore likely to have high affinity for the epitope.

To determine the HLA restriction of the P703P response, a panel of antigen presenting cells (APC) was generated that was partially matched with the donor used to generate the T cells. The APC were pulsed with the peptide and used in proliferation and cytokine assays together with line 1-F9. APC matched with the donor at HLA-DRB0701 and HLA-DQB02 alleles were able to present the peptide to the T cells, indicating that the P703P-specific response is restricted to one of these alleles.

Antibody blocking assays were utilized to determine if the restricting allele was HLA-DR0701 or HLA-DQ02. The anti-HLA-DR blocking antibody L243 or an irrelevant isotype matched IgG2a were added to T cells and APC cultures pulsed with the peptide RMPTVLQCVNVS VVS (SEQ ID NO: 638) at 250 ng/ml. Standard interferon-gamma and proliferation assays were performed. Whereas the control antibody had no effect on the ability of the T cells to recognize peptide-pulsed APC, in both assays the anti-HLA-DR antibody completely blocked the ability of the T cells to specifically recognize peptide-pulsed APC.

To determine if the peptide epitope RMPTVLQCVNVS VVS (SEQ ID NO: 638) was naturally processed, the ability of line 1-F9 to recognize APC pulsed with recombinant P703P protein was examined. For these experiments a number of

recombinant P703P sources were utilized: *E. coli*-derived P703P, Pichia-derived P703P and baculovirus-derived P703P. Irrelevant protein controls used were *E. coli*-derived L3E (a lung-specific antigen) and baculovirus-derived mammaglobin. In interferon-gamma ELISA assays, line 1-F9 was able to efficiently recognize both *E. coli* forms of P703P as well as Pichia-derived recombinant P703P, while baculovirus-derived P703P was recognized less efficiently. Subsequent Western blot analysis revealed that the *E. coli* and Pichia P703P protein preparations were intact while the baculovirus P703P preparation was approximately 75% degraded. Thus, peptide RMPTVLQCVNVSVVS (SEQ ID NO: 638) from P703P is a naturally processed peptide epitope derived from P703P and presented to T cells in the context of HLA-DRB-0701

In further studies, twenty-four 15-mer peptides overlapping by 10 amino acids and derived from the N-terminal fragment of P703P (corresponding to amino acids 27-154 of SEQ ID NO: 525) were generated by standard procedures and their ability to be recognized by CD4 cells was determined essentially as described above. DC were pulsed overnight with pools of the peptides with each peptide at a final concentration of 10 microgram/ml. A large number of individual CD4 T cell lines (65/480) demonstrated significant proliferation and cytokine release (IFN-gamma) in response to the P703P peptide pools but not to a control peptide pool. The CD4 T cell lines which demonstrated specific activity were restimulated on the appropriate pool of P703P peptides and reassayed on the individual peptides of each pool as well as a peptide dose titration of the pool of peptides in a IFN-gamma release assay and in a proliferation assay.

Sixteen immunogenic peptides were recognized by the T cells from the entire set of peptide antigens tested. The amino acid sequences of these peptides are provided in SEQ ID NO: 656-671, with the corresponding cDNA sequences being provided in SEQ ID NO: 640-655, respectively. In some cases the peptide reactivity of the T cell line could be mapped to a single peptide, however some could be mapped to more than one peptide in each pool. Those CD4 T cell lines that displayed a representative pattern of recognition from each peptide pool with a reasonable affinity for peptide were chosen for further analysis (I-1A, -6A; II-4C, -5E; III-6E, IV-4B, -3F, -9B, -10F, V-5B, -4D, and -10F). These CD4 T cell lines were restimulated on the

appropriate individual peptide and reassayed on autologous DC pulsed with a truncated form of recombinant P703P protein made in *E. coli* (a.a. 96 - 254 of SEQ ID NO: 525), full-length P703P made in the baculovirus expression system, and a fusion between influenza virus NS1 and P703P made in *E. coli*. Of the T cell lines tested, line I-1A  
5 recognized specifically the truncated form of P703P (*E. coli*) but no other recombinant form of P703P. This line also recognized the peptide used to elicit the T cells. Line 2-4C recognized the truncated form of P703P (*E. coli*) and the full length form of P703P made in baculovirus, as well as peptide. The remaining T cell lines tested were either peptide-specific only (II-5E, II-6F, IV-4B, IV-3F, IV-9B, IV-10F, V-5B and V-4D) or  
10 were non-responsive to any antigen tested (V-10F). These results demonstrate that the peptide sequence RPLLANDLMLIKLDE (SEQ ID NO: 671; corresponding to a.a. 110-124 of SEQ ID NO: 525) recognized by the T cell line I-1A, and the peptide sequences SVSESDTIRSISIAS (SEQ ID NO: 668; corresponding to a.a. 125-139 of SEQ ID NO: 525) and ISIASQCPTAGNSCL (SEQ ID NO: 667; corresponding to a.a. 135-149 of  
15 SEQ ID NO: 525) recognized by the T cell line II-4C may be naturally processed epitopes of the P703P protein.

### EXAMPLE 11

#### EXPRESSION OF A BREAST TUMOR-DERIVED ANTIGEN

20

#### IN PROSTATE

Isolation of the antigen B305D from breast tumor by differential display is described in US Patent Application No. 08/700,014, filed August 20, 1996. Several different splice forms of this antigen were isolated. The determined cDNA sequences  
25 for these splice forms are provided in SEQ ID NO: 366-375, with the predicted amino acid sequences corresponding to the sequences of SEQ ID NO: 292, 298 and 301-303 being provided in SEQ ID NO: 299-306, respectively. In further studies, a splice variant of the cDNA sequence of SEQ ID NO: 366 was isolated which was found to contain an additional guanine residue at position 884 (SEQ ID NO: 530), leading to a  
30 frameshift in the open reading frame. The determined DNA sequence of this ORF is



provided in SEQ ID NO: 531. This frameshift generates a protein sequence (provided in SEQ ID NO: 532) of 293 amino acids that contains the C-terminal domain common to the other isoforms of B305D but that differs in the N-terminal region.

The expression levels of B305D in a variety of tumor and normal tissues were examined by real time PCR and by Northern analysis. The results indicated that B305D is highly expressed in breast tumor, prostate tumor, normal prostate and normal testes, with expression being low or undetectable in all other tissues examined (colon tumor, lung tumor, ovary tumor, and normal bone marrow, colon, kidney, liver, lung, ovary, skin, small intestine, stomach). Using real-time PCR on a panel of prostate tumors, expression of B305D in prostate tumors was shown to increase with increasing Gleason grade, demonstrating that expression of B305D increases as prostate cancer progresses.

#### EXAMPLE 12

##### 15 GENERATION OF HUMAN CTL *IN VITRO* USING WHOLE GENE PRIMING AND STIMULATION TECHNIQUES WITH THE PROSTATE-SPECIFIC ANTIGEN P501S

Using *in vitro* whole-gene priming with P501S-vaccinia infected DC (see, for example, Yee et al, *The Journal of Immunology*, 157(9):4079-86, 1996), human CTL lines were derived that specifically recognize autologous fibroblasts transduced with P501S (also known as L1-12), as determined by interferon- $\gamma$  ELISPOT analysis as described above. Using a panel of HLA-mismatched B-LCL lines transduced with P501S, these CTL lines were shown to be likely restricted to HLAB class I allele. Specifically, dendritic cells (DC) were differentiated from monocyte cultures derived from PBMC of normal human donors by growing for five days in RPMI medium containing 10% human serum, 50 ng/ml human GM-CSF and 30 ng/ml human IL-4. Following culture, DC were infected overnight with recombinant P501S vaccinia virus at a multiplicity of infection (M.O.I) of five, and matured overnight by the addition of 3  $\mu$ g/ml CD40 ligand. Virus was inactivated by UV irradiation. CD8+ T cells were isolated using a magnetic bead system, and priming cultures were initiated

using standard culture techniques. Cultures were restimulated every 7-10 days using autologous primary fibroblasts retrovirally transduced with P501S and CD80. Following four stimulation cycles, CD8+ T cell lines were identified that specifically produced interferon- $\gamma$  when stimulated with P501S and CD80-transduced autologous  
5 fibroblasts. A panel of HLA-mismatched B-LCL lines transduced with P501S were generated to define the restriction allele of the response. By measuring interferon- $\gamma$  in an ELISPOT assay, the P501S specific response was shown to be likely restricted by HLA B alleles. These results demonstrate that a CD8+ CTL response to P501S can be elicited.

10 To identify the epitope(s) recognized, cDNA encoding P501S was fragmented by various restriction digests, and sub-cloned into the retroviral expression vector pBIB-KS. Retroviral supernatants were generated by transfection of the helper packaging line Phoenix-Ampho. Supernatants were then used to transduce Jurkat/A2Kb cells for CTL screening. CTL were screened in IFN- $\gamma$  ELISPOT  
15 assays against these A2Kb targets transduced with the "library" of P501S fragments. Initial positive fragments P501S/H3 and P501S/F2 were sequenced and found to encode amino acids 106-553 and amino acids 136-547, respectively, of SEQ ID NO: 113. A truncation of H3 was made to encode amino acid residues 106-351 of SEQ ID NO: 113, which was unable to stimulate the CTL, thus localizing the epitope to amino acid  
20 residues 351-547. Additional fragments encoding amino acids 1-472 (Fragment A) and amino acids 1-351 (Fragment B) were also constructed. Fragment A but not Fragment B stimulated the CTL thus localizing the epitope to amino acid residues 351-472. Overlapping 20-mer and 18-mer peptides representing this region were tested by pulsing Jurkat/A2Kb cells versus CTL in an IFN- $\gamma$  assay. Only peptides P501S-369(20)  
25 and P501S-369(18) stimulated the CTL. Nine-mer and 10-mer peptides representing this region were synthesized and similarly tested. Peptide P501S-370 (SEQ ID NO: 539) was the minimal 9-mer giving a strong response. Peptide P501S-376 (SEQ ID NO: 540) also gave a weak response, suggesting that it might represent a cross-reactive epitope.

In subsequent studies, the ability of primary human B cells transduced with P501S to prime MHC class I-restricted, P501S-specific, autologous CD8 T cells was examined. Primary B cells were derived from PBMC of a homozygous HLA-A2 donor by culture in CD40 ligand and IL-4, transduced at high frequency with recombinant P501S in the vector pBIB, and selected with blastocidin-S. For *in vitro* priming, purified CD8+ T cells were cultured with autologous CD40 ligand + IL-4 derived, P501S-transduced B cells in a 96-well microculture format. These CTL microcultures were re-stimulated with P501S-transduced B cells and then assayed for specificity. Following this initial screen, microcultures with significant signal above background were cloned on autologous EBV-transformed B cells (BLCL), also transduced with P501S. Using IFN-gamma ELISPOT for detection, several of these CD8 T cell clones were found to be specific for P501S, as demonstrated by reactivity to BLCL/P501S but not BLCL transduced with control antigen. It was further demonstrated that the anti-P501S CD8 T cell specificity is HLA-A2-restricted. First, antibody blocking experiments with anti-HLA-A,B,C monoclonal antibody (W6.32), anti-HLA-B,C monoclonal antibody (B1.23.2) and a control monoclonal antibody showed that only the anti-HLA-A,B,C antibody blocked recognition of P501S-expressing autologous BLCL. Secondly, the anti-P501S CTL also recognized an HLA-A2 matched, heterologous BLCL transduced with P501S, but not the corresponding EGFP transduced control BLCL.

A naturally processed, CD8, class I-restricted peptide epitope of P501S was identified as follows. Dendritic Cells (DC) were isolated by Percol gradient followed by differential adherence, and cultured for 5 days in the presence of RPMI medium containing 1% human serum, 50ng/ml GM-CSF and 30ng/ml IL-4. Following culture, DC were infected for 24 hours with P501S-expressing adenovirus at an MOI of 10 and matured for an additional 24 hours by the addition of 2ug/ml CD40 ligand. CD8 cells were enriched for by the subtraction of CD4+, CD14+ and CD16+ populations from PBMC with magnetic beads. Priming cultures containing 10,000 P501S-expressing DC and 100,000 CD8+ T cells per well were set up in 96-well V-bottom plates with RPMI containing 10% human serum, 5ng/ml IL-12 and 10ng/ml IL-6. Cultures were stimulated every 7 days using autologous fibroblasts retrovirally

transduced to express P501S and CD80, and were treated with IFN-gamma for 48-72 hours to upregulate MHC Class I expression. 10u/ml IL-2 was added at the time of stimulation and on days 2 and 5 following stimulation. Following 4 stimulation cycles, one P501S-specific CD8<sup>+</sup> T cell line (referred to as 2A2) was identified that produced  
5 IFN-gamma in response to IFN-gamma-treated P501S/CD80 expressing autologous fibroblasts, but not in response to IFN-gamma-treated P703P/CD80 expressing autologous fibroblasts in a  $\gamma$ -IFN Elispot assay. Line 2A2 was cloned in 96-well plates with 0.5 cell/well or 2 cells/well in the presence of 75,000 PBMC/well, 10,000 B-LCL/well, 30ng/ml OKT3 and 50u/ml IL-2. Twelve clones were isolated that showed  
10 strong P501S specificity in response to transduced fibroblasts.

Fluorescence activated cell sorting (FACS) analysis was performed on P501S-specific clones using CD3-, CD4- and CD8-specific antibodies conjugated to PercP, FITC and PE respectively. Consistent with the use of CD8 enriched T cells in the priming cultures, P5401S-specific clones were determined to be CD3<sup>+</sup>, CD8<sup>+</sup> and  
15 CD4<sup>-</sup>.

To identify the relevant P501S epitope recognized by P501S specific CTL, pools of 18-20 mer or 30-mer peptides that spanned the majority of the amino acid sequence of P501S were loaded onto autologous B-LCL and tested in  $\gamma$ -IFN Elispot assays for the ability to stimulate two P501S-specific CTL clones, referred to as 4E5  
20 and 4E7. One pool, composed of five 18-20 mer peptides that spanned amino acids 411-486 of P501S (SEQ ID NO: 113), was found to be recognized by both P501S-specific clones. To identify the specific 18-20 mer peptide recognized by the clones, each of the 18-20 mer peptides that comprised the positive pool were tested individually in  $\gamma$ -IFN Elispot assays for the ability to stimulate the two P501S-specific CTL clones, 4E5 and  
25 4E7. Both 4E5 and 4E7 specifically recognized one 20-mer peptide (SEQ ID NO: 710; cDNA sequence provided in SEQ ID NO: 711) that spanned amino acids 453-472 of P501S. Since the minimal epitope recognized by CD8<sup>+</sup> T cells is almost always either a 9 or 10-mer peptide sequence, 10-mer peptides that spanned the entire sequence of SEQ ID NO: 710 were synthesized that differed by 1 amino acid. Each of these 10-mer  
30 peptides was tested for the ability to stimulate two P501S-specific clones, (referred to as 1D5 and 1E12). One 10-mer peptide (SEQ ID NO: 712; cDNA sequence provided in

SEQ ID NO: 713) was identified that specifically stimulated the P501S-specific clones. This epitope spans amino acids 463-472 of P501S. This sequence defines a minimal 10-mer epitope from P501S that can be naturally processed and to which CTL responses can be identified in normal PBMC. Thus, this epitope is a candidate for use as a vaccine moiety, and as a therapeutic and/or diagnostic reagent for prostate cancer.

To identify the class I restriction element for the P501S-derived sequence of SEQ ID NO: 712, HLA blocking and mismatch analyses were performed. In  $\gamma$ -IFN Elispot assays, the specific response of clones 4A7 and 4E5 to P501S-transduced autologous fibroblasts was blocked by pre-incubation with 25ug/ml W6/32 (pan-Class I blocking antibody) and B1.23.2 (HLA-B/C blocking antibody). These results demonstrate that the SEQ ID NO: 712-specific response is restricted to an HLA-B or HLA-C allele.

For the HLA mismatch analysis, autologous B-LCL (HLA-A1,A2,B8,B51, Cw1, Cw7) and heterologous B-LCL (HLA-A2,A3,B18,B51,Cw5,Cw14) that share the HLAB51 allele were pulsed for one hour with 20ug/ml of peptide of SEQ ID NO: 712, washed, and tested in  $\gamma$ -IFN Elispot assays for the ability to stimulate clones 4A7 and 4E5. Antibody blocking assays with the B1.23.2 (HLA-B/C blocking antibody) were also performed. SEQ ID NO: 712-specific response was detected using both the autologous (D326) and heterologous (D107) B-LCL, and furthermore the responses were blocked by pre-incubation with 25ug/ml of B1.23.2 HLA-B/C blocking antibody. Together these results demonstrate that the P501S-specific response to the peptide of SEQ ID NO: 712 is restricted to the HLA-B51 class I allele. Molecular cloning and sequence analysis of the HLA-B51 allele from D3326 revealed that the HLA-B51 subtype of D326 is HLA-B51011.

Based on the 10-mer P501S-derived epitope of SEQ ID NO: 712, two 9-mers with the sequences of SEQ ID NO: 714 and 715 were synthesized and tested in Elispot assays for the ability to stimulate two P501S-specific CTL clones derived from line 2A2. The 10-mer peptide of SEQ ID NO: 712, as well as the 9-mer peptide of SEQ ID NO: 715, but not the 9-mer peptide of SEQ ID NO: 714, were capable of stimulating the P501S-specific CTL to produce IFN-gamma. These results demonstrate that the peptide of SEQ ID NO: 715 is a 9-mer P501S-derived epitope recognized by P501S-

specific CTL. The DNA sequence encoding the epitope of SEQ ID NO: 715 is provided in SEQ ID NO: 716.

To identify the class I restricting allele for the P501S-derived peptide of SEQ ID NO: 712 and 715 specific response, each of the HLA B and C alleles were  
5 cloned from the donor used in the *in vitro* priming experiment. Sequence analysis indicated that the relevant alleles were HLA-B8, HLA-B51, HLA-Cw01 and HLA-Cw07. Each of these alleles were subcloned into an expression vector and co-transfected together with the P501S gene into VA-13 cells. Transfected VA-13 cells were then tested for the ability to specifically stimulate the P501S-specific CTL in  
10 ELISPOT assays. VA-13 cells transfected with P501S and HLA-B51 were capable of stimulating the P501S-specific CTL to secrete gamma-IFN. VA-13 cells transfected with HLA-B51 alone or P501S + the other HLA-alleles were not capable of stimulating the P501S-specific CTL. These results demonstrate that the restricting allele for the P501S-specific response is the HLAB51 allele. Sequence analysis revealed that the  
15 subtype of the relevant restricting allele is HLA-B51011.

To determine if the P501S-specific CTL could recognize prostate tumor cells that express P501S, the P501S-positive lines LnCAP and CRL2422 (both expressing "moderate" amounts of P501S mRNA and protein), and PC-3 (expressing low amounts of P501S mRNA and protein), plus the P501S-negative cell line DU-145  
20 were retrovirally transduced with the HLA-B51011 allele that was cloned from the donor used to generate the P501S-specific CTL. HLA-B51011- or EGFP-transduced and selected tumor cells were treated with gamma-interferon and androgen (to upregulate stimulatory functions and P501S, respectively) and used in gamma-interferon Elispot assays with the P501S-specific CTL clones 4E5 and 4E7. Untreated  
25 cells were used as a control.

Both 4E5 and 4E7 efficiently and specifically recognized LnCAP and CRL2422 cells that were transduced with the HLA-B51011 allele, but not the same cell lines transduced with EGFP. Additionally, both CTL clones specifically recognized PC-3 cells transduced with HLA-B51011, but not the P501S-negative tumor cell line  
30 DU-145. Treatment with gamma-interferon or androgen did not enhance the ability of CTL to recognize tumor cells. These results demonstrate that P501S-specific CTL,

generated by *in vitro* whole gene priming, specifically and efficiently recognize prostate tumor cell lines that express P501S.

A naturally processed CD4 epitope of P501S was identified as follows.

CD4 cells specific for P501S were prepared as described above. A series  
5 of 16 overlapping peptides were synthesized that spanned approximately 50% of the amino terminal portion of the P501S gene (amino acids 1- 325 of SEQ ID NO: 113). For priming, peptides were combined into pools of 4 peptides, pulsed at 4 µg/ml onto dendritic cells (DC) for 24 hours, with TNF-alpha. DC were then washed and mixed with negatively selected CD4+ T cells in 96 well U-bottom plates. Cultures were re-  
10 stimulated weekly on fresh DC loaded with peptide pools. Following a total of 4 stimulation cycles, cells were rested for an additional week and tested for specificity to APC pulsed with peptide pools using γ-IFN ELISA and proliferation assays. For these assays, adherent monocytes loaded with either the relevant peptide pool at 4ug/ml or an irrelevant peptide at µg/ml were used as APC. T cell lines that demonstrated either  
15 specific cytokine secretion or proliferation were then tested for recognition of individual peptides that were present in the pool. T cell lines could be identified from pools A and B that recognized individual peptides from these pools.

From pool A, lines AD9 and AE10 specifically recognized peptide 1 (SEQ ID NO: 719), and line AF5 recognized peptide 39 (SEQ ID NO: 718). From pool B, line BC6 could be identified that recognized peptide 58 (SEQ ID NO: 717). Each of these lines were stimulated on the specific peptide and tested for specific recognition of the peptide in a titration assay as well as cell lysates generated by infection of HEK 293 cells with adenovirus expressing either P501S or an irrelevant antigen. For these assays, APC-adherent monocytes were pulsed with either 10, 1, or 0.1 µg/ml individual P501S peptides, and DC were pulsed overnight with a 1:5 dilution of adenovirally infected cell lysates. Lines AD9, AE10 and AF5 retained significant recognition of the relevant P501S-derived peptides even at 0.1 mg/ml. Furthermore, line AD9 demonstrated significant (8.1 fold stimulation index) specific activity for lysates from adenovirus-P501S infected cells. These results demonstrate that high affinity CD4 T cell lines can be generated toward P501S-derived epitopes, and that at least a subset of these T cells specific for the P501S derived sequence of SEQ ID NO: 719 are specific for an epitope that is naturally processed by human cells. The DNA sequences encoding the amino acid sequences of SEQ ID NO: 717-719 are provided in SEQ ID NO: 720-722, respectively.

To further characterize the P501S-specific activity of AD9, the line was cloned using anti-CD3. Three clones, referred to as 1A1, 1A9 and 1F5, were identified that were specific for the P501S-1 peptide (SEQ ID NO: 719). To determine the HLA restriction allele for the P501S-specific response, each of these clones was tested in class II antibody blocking and HLA mismatch assays using proliferation and gamma-interferon assays. In antibody blocking assays and measuring gamma-interferon production using ELISA assays, the ability of all three clones to recognize peptide pulsed APC was specifically blocked by co-incubation with either a pan-class II blocking antibody or a HLA-DR blocking antibody, but not with a HLA-DQ or an irrelevant antibody. Proliferation assays performed simultaneously with the same cells confirmed these results. These data indicate that the P501S-specific response of the clones is restricted by an HLA-DR allele. Further studies demonstrated that the restricting allele for the P501S-specific response is HLA-DRB1501.



## EXAMPLE 13

IDENTIFICATION OF PROSTATE-SPECIFIC ANTIGENS  
BY MICROARRAY ANALYSIS

5           This Example describes the isolation of certain prostate-specific polypeptides from a prostate tumor cDNA library.

          A human prostate tumor cDNA expression library as described above was screened using microarray analysis to identify clones that display at least a three fold over-expression in prostate tumor and/or normal prostate tissue, as compared to  
10 non-prostate normal tissues (not including testis). 372 clones were identified, and 319 were successfully sequenced. Table I presents a summary of these clones, which are shown in SEQ ID NOs:385-400. Of these sequences SEQ ID NOs:386, 389, 390 and 392 correspond to novel genes, and SEQ ID NOs: 393 and 396 correspond to previously identified sequences. The others (SEQ ID NOs:385, 387, 388, 391, 394, 395 and 397-  
15 400) correspond to known sequences, as shown in Table I.

Table I  
Summary of Prostate Tumor Antigens

Known Genes	Previously Identified Genes	Novel Genes
T-cell gamma chain	P504S	23379 (SEQ ID NO:389)
Kallikrein	P1000C	23399 (SEQ ID NO:392)
Vector	P501S	23320 (SEQ ID NO:386)
CGI-82 protein mRNA (23319; SEQ ID NO:385)	P503S	23381 (SEQ ID NO:390)
PSA	P510S	
Ald. 6 Dehyd.	P784P	
L-iditol-2 dehydrogenase (23376; SEQ ID NO:388)	P502S	
Ets transcription factor PDEF (22672; SEQ ID NO:398)	P706P	
hTGR (22678; SEQ ID NO:399)	19142.2, bangur.seq (22621; SEQ ID NO:396)	
KIAA0295(22685; SEQ ID NO:400)	5566.1 Wang (23404; SEQ ID NO:393)	
Prostatic Acid Phosphatase(22655; SEQ ID NO:397)	P712P	
transglutaminase (22611; SEQ ID NO:395)	P778P	
HDLBP (23508; SEQ ID NO:394)		
CGI-69 Protein(23367; SEQ ID NO:387)		
KIAA0122(23383; SEQ ID NO:391)		
TEEG		

CGI-82 showed 4.06 fold over-expression in prostate tissues as compared to other normal tissues tested. It was over-expressed in 43% of prostate tumors, 25% normal prostate, not detected in other normal tissues tested. L-iditol-2 dehydrogenase showed 4.94 fold over-expression in prostate tissues as compared to other normal tissues tested. It was over-expressed in 90% of prostate tumors, 100% of normal prostate, and not detected in other normal tissues tested. Ets transcription factor PDEF showed 5.55 fold over-expression in prostate tissues as compared to other normal tissues tested. It was over-expressed in 47% prostate tumors, 25% normal prostate and not detected in other normal tissues tested. hTGR1 showed 9.11 fold over-expression in prostate tissues as compared to other normal tissues tested. It was over-expressed in 63% of prostate tumors and is not detected in normal tissues tested including normal prostate. KIAA0295 showed 5.59 fold over-expression in prostate tissues as compared to other normal tissues tested. It was over-expressed in 47% of prostate tumors, low to undetectable in normal tissues tested including normal prostate tissues. Prostatic acid phosphatase showed 9.14 fold over-expression in prostate tissues as compared to other normal tissues tested. It was over-expressed in 67% of prostate tumors, 50% of normal prostate, and not detected in other normal tissues tested. Transglutaminase showed 14.84 fold over-expression in prostate tissues as compared to other normal tissues tested. It was over-expressed in 30% of prostate tumors, 50% of normal prostate, and is not detected in other normal tissues tested. High density lipoprotein binding protein (HDLBP) showed 28.06 fold over-expression in prostate tissues as compared to other normal tissues tested. It was over-expressed in 97% of prostate tumors, 75% of normal prostate, and is undetectable in all other normal tissues tested. CGI-69 showed 3.56 fold over-expression in prostate tissues as compared to other normal tissues tested. It is a low abundant gene, detected in more than 90% of prostate tumors, and in 75% normal prostate tissues. The expression of this gene in normal tissues was very low. KIAA0122 showed 4.24 fold over-expression in prostate tissues as compared to other normal tissues tested. It was over-expressed in 57% of prostate tumors, it was undetectable in all normal tissues tested including normal prostate tissues. 19142.2 bangur showed 23.25 fold over-expression in prostate tissues as compared to other

normal tissues tested. It was over-expressed in 97% of prostate tumors and 100% of normal prostate. It was undetectable in other normal tissues tested. 5566.1 Wang showed 3.31 fold over-expression in prostate tissues as compared to other normal tissues tested. It was over-expressed in 97% of prostate tumors, 75% normal prostate and was also over-expressed in normal bone marrow, pancreas, and activated PBMC. Novel clone 23379 (also referred to as P553S) showed 4.86 fold over-expression in prostate tissues as compared to other normal tissues tested. It was detectable in 97% of prostate tumors and 75% normal prostate and is undetectable in all other normal tissues tested. Novel clone 23399 showed 4.09 fold over-expression in prostate tissues as compared to other normal tissues tested. It was over-expressed in 27% of prostate tumors and was undetectable in all normal tissues tested including normal prostate tissues. Novel clone 23320 showed 3.15 fold over-expression in prostate tissues as compared to other normal tissues tested. It was detectable in all prostate tumors and 50% of normal prostate tissues. It was also expressed in normal colon and trachea. Other normal tissues do not express this gene at high level.

Subsequent full-length cloning studies on P553S, using standard techniques, revealed that this clone is an incomplete spliced form of P501S. The determined cDNA sequences for four splice variants of P553S are provided in SEQ ID NO: 623-626. An amino acid sequence encoded by SEQ ID NO: 626 is provided in SEQ ID NO: 627. The cDNA sequence of SEQ ID NO: 623 was found to contain two open reading frames (ORFs). The amino acid sequences encoded by these two ORFs are provided in SEQ ID NO: 628 and 629.

#### EXAMPLE 14

##### IDENTIFICATION OF PROSTATE-SPECIFIC ANTIGENS BY ELECTRONIC SUBTRACTION

This Example describes the use of an electronic subtraction technique to identify prostate-specific antigens.

Potential prostate-specific genes present in the GenBank human EST database were identified by electronic subtraction (similar to that described by Vasmatizis et al., *Proc. Natl. Acad. Sci. USA* 95:300-304, 1998). The sequences of EST clones (43,482) derived from various prostate libraries were obtained from the GenBank public human EST database. Each prostate EST sequence was used as a query sequence in a BLASTN (National Center for Biotechnology Information) search against the human EST database. All matches considered identical (length of matching sequence >100 base pairs, density of identical matches over this region > 70%) were grouped (aligned) together in a cluster. Clusters containing more than 200 ESTs were discarded since they probably represented repetitive elements or highly expressed genes such as those for ribosomal proteins. If two or more clusters shared common ESTs, those clusters were grouped together into a "supercluster," resulting in 4,345 prostate superclusters.

Records for the 479 human cDNA libraries represented in the GenBank release were downloaded to create a database of these cDNA library records. These 479 cDNA libraries were grouped into three groups: Plus (normal prostate and prostate tumor libraries, and breast cell line libraries, in which expression was desired), Minus (libraries from other normal adult tissues, in which expression was not desirable), and Other (libraries from fetal tissue, infant tissue, tissues found only in women, non-prostate tumors and cell lines other than prostate cell lines, in which expression was considered to be irrelevant). A summary of these library groups is presented in Table II.

Table II  
Prostate cDNA Libraries and ESTs

Library	# of Libraries	# of ESTs
Plus	25	43,482
Normal	11	18,875
Tumor	11	21,769
Cell lines	3	2,838
Minus	166	
Other	287	

5                Each supercluster was analyzed in terms of the ESTs within the supercluster. The tissue source of each EST clone was noted and used to classify the superclusters into four groups: Type 1- EST clones found in the Plus group libraries only; no expression detected in Minus or Other group libraries; Type 2- EST clones derived from the Plus and Other group libraries only; no expression detected in the

10 Minus group; Type 3- EST clones derived from the Plus, Minus and Other group libraries, but the number of ESTs derived from the Plus group is higher than in either the Minus or Other groups; and Type 4- EST clones derived from Plus, Minus and Other group libraries, but the number derived from the Plus group is higher than the number derived from the Minus group. This analysis identified 4,345 breast clusters

15 (see Table III). From these clusters, 3,172 EST clones were ordered from Research Genetics, Inc., and were received as frozen glycerol stocks in 96-well plates.

Table III  
Prostate Cluster Summary

Type	# of Superclusters	# of ESTs Ordered
1	688	677
2	2899	2484
3	85	11
4	673	0
Total	4345	3172

5           The EST clone inserts were PCR-amplified using amino-linked PCR  
primers for Synteni microarray analysis. When more than one PCR product was  
obtained for a particular clone, that PCR product was not used for expression analysis.  
In total, 2,528 clones from the electronic subtraction method were analyzed by  
microarray analysis to identify electronic subtraction breast clones that had high levels  
10 of tumor vs. normal tissue mRNA. Such screens were performed using a Synteni (Palo  
Alto, CA) microarray, according to the manufacturer's instructions (and essentially as  
described by Schena et al., *Proc. Natl. Acad. Sci. USA* 93:10614-10619, 1996 and  
Heller et al., *Proc. Natl. Acad. Sci. USA* 94:2150-2155, 1997). Within these analyses,  
the clones were arrayed on the chip, which was then probed with fluorescent probes  
15 generated from normal and tumor prostate cDNA, as well as various other normal  
tissues. The slides were scanned and the fluorescence intensity was measured.

Clones with an expression ratio greater than 3 (*i.e.*, the level in prostate  
tumor and normal prostate mRNA was at least three times the level in other normal  
tissue mRNA) were identified as prostate tumor-specific sequences (Table IV). The  
20 sequences of these clones are provided in SEQ ID NO: 401-453, with certain novel  
sequences shown in SEQ ID NO: 407, 413, 416-419, 422, 426, 427 and 450.

Table IV

Prostate-tumor Specific Clones

SEQ ID NO.	Sequence Designation	Comments
401	22545	previously identified P1000C
402	22547	previously identified P704P
403	22548	known
404	22550	known
405	22551	PSA
406	22552	prostate secretory protein 94
407	22553	novel
408	22558	previously identified P509S
409	22562	glandular kallikrein
410	22565	previously identified P1000C
411	22567	PAP
412	22568	B1006C (breast tumor antigen)
413	22570	novel
414	22571	PSA
415	22572	previously identified P706P
416	22573	novel
417	22574	novel
418	22575	novel
419	22580	novel
420	22581	PAP
421	22582	prostatic secretory protein 94
422	22583	novel
423	22584	prostatic secretory protein 94
424	22585	prostatic secretory protein 94
425	22586	known
426	22587	novel
427	22588	novel
428	22589	PAP
429	22590	known
430	22591	PSA
431	22592	known
432	22593	Previously identified P777P
433	22594	T cell receptor gamma chain
434	22595	Previously identified P705P
435	22596	Previously identified P707P
436	22847	PAP
437	22848	known
438	22849	prostatic secretory protein 57



439	22851	PAP
440	22852	PAP
441	22853	PAP
442	22854	previously identified P509S
443	22855	previously identified P705P
444	22856	previously identified P774P
445	22857	PSA
446	23601	previously identified P777P
447	23602	PSA
448	23605	PSA
449	23606	PSA
450	23612	novel
451	23614	PSA
452	23618	previously identified P1000C
453	23622	previously identified P705P

Further studies on the clone of SEQ ID NO: 407 (also referred to as P1020C) led to the isolation of an extended cDNA sequence provided in SEQ ID NO: 591. This extended cDNA sequence was found to contain an open reading frame that encodes the predicted amino acid sequence of SEQ ID NO: 592. The P1020C cDNA and amino acid sequences were found to show some similarity to the human endogenous retroviral HERV-K pol gene and protein.

#### EXAMPLE 15

##### 10 FURTHER IDENTIFICATION OF PROSTATE-SPECIFIC ANTIGENS BY MICROARRAY ANALYSIS

This Example describes the isolation of additional prostate-specific polypeptides from a prostate tumor cDNA library.

A human prostate tumor cDNA expression library as described above was screened using microarray analysis to identify clones that display at least a three fold over-expression in prostate tumor and/or normal prostate tissue, as compared to non-prostate normal tissues (not including testis). 142 clones were identified and sequenced. Certain of these clones are shown in SEQ ID NO: 454-467. Of these sequences, SEQ ID NO: 459-460 represent novel genes. The others (SEQ ID NO: 454-20 458 and 461-467) correspond to known sequences. Comparison of the determined

cDNA sequence of SEQ ID NO: 461 with sequences in the Genbank database using the BLAST program revealed homology to the previously identified transmembrane protease serine 2 (TMPRSS2). The full-length cDNA sequence for this clone is provided in SEQ ID NO: 751, with the corresponding amino acid sequence being  
5 provided in SEQ ID NO: 752. The cDNA sequence encoding the first 209 amino acids of TMPRSS2 is provided in SEQ ID NO: 753, with the first 209 amino acids being provided in SEQ ID NO: 754.

The sequence of SEQ ID NO: 462 (referred to as P835P) was found to correspond to the previously identified clone FLJ13518 (Accession AK023643; SEQ ID  
10 NO: 774), which had no associated open reading frame (ORF). This clone was used to search the Geneseq DNA database and matched a clone previously identified as a G protein-coupled receptor protein (DNA Geneseq Accession A09351; amino acid Geneseq Accession Y92365), that is characterized by the presence of seven transmembrane domains. The sequences of fragments between these domains are  
15 provided in SEQ ID NO: 778-785, with SEQ ID NO: 778, 780, 782 and 784 representing extracellular domains and SEQ ID NO: 779, 781, 783 and 785 representing intracellular domains. SEQ ID NO: 778-785 represent amino acids 1-28, 53-61, 83-103, 124-143, 165-201, 226-238, 263-272 and 297-381, respectively, of P835P. The full-length cDNA sequence for P835P is provided in SEQ ID NO: 773. The cDNA  
20 sequence of the open reading frame for P835P, including stop codon, is provided in SEQ ID NO: 775, with the open reading frame without stop codon being provided in SEQ ID NO: 776 and the corresponding amino acid sequence being provided in SEQ ID NO: 777.

25

## EXAMPLE 16

## FURTHER CHARACTERIZATION OF PROSTATE-SPECIFIC ANTIGEN P710P

This Example describes the full length cloning of P710P.

The prostate cDNA library described above was screened with the P710P  
30 fragment described above. One million colonies were plated on LB/Ampicillin plates.

Nylon membrane filters were used to lift these colonies, and the cDNAs picked up by these filters were then denatured and cross-linked to the filters by UV light. The P710P fragment was radiolabeled and used to hybridize with the filters. Positive cDNA clones were selected and their cDNAs recovered and sequenced by an automatic Perkin Elmer/Applied Biosystems Division Sequencer. Four sequences were obtained, and are presented in SEQ ID NO: 468-471. These sequences appear to represent different splice variants of the P710P gene. Subsequent comparison of the cDNA sequences of P710P with those in Genbank revealed homology to the DD3 gene (Genbank accession numbers AF103907 & AF103908). The cDNA sequence of DD3 is provided in SEQ ID NO: 618.

#### EXAMPLE 17

##### PROTEIN EXPRESSION OF PROSTATE-SPECIFIC ANTIGENS

This example describes the expression and purification of prostate-specific antigens in *E. coli*, baculovirus, mammalian and yeast cells.

##### a) Expression of P501S in *E. coli*

Expression of the full-length form of P501S was attempted by first cloning P501S without the leader sequence (amino acids 36-553 of SEQ ID NO: 113) downstream of the first 30 amino acids of the *M. tuberculosis* antigen Ra12 (SEQ ID NO: 484) in pET17b. Specifically, P501S DNA was used to perform PCR using the primers AW025 (SEQ ID NO: 485) and AW003 (SEQ ID NO: 486). AW025 is a sense cloning primer that contains a HindIII site. AW003 is an antisense cloning primer that contains an EcoRI site. DNA amplification was performed using 5 µl 10X Pfu buffer, 1 µl 20 mM dNTPs, 1 µl each of the PCR primers at 10 µM concentration, 40 µl water, 1 µl Pfu DNA polymerase (Stratagene, La Jolla, CA) and 1 µl DNA at 100 ng/µl. Denaturation at 95°C was performed for 30 sec, followed by 10 cycles of 95°C for 30 sec, 60°C for 1 min and by 72°C for 3 min. 20 cycles of 95°C for 30 sec, 65°C for 1 min and by 72°C for 3 min, and lastly by 1 cycle of 72°C for 10 min. The PCR product was

cloned to Ra12m/pET17b using HindIII and EcoRI. The sequence of the resulting fusion construct (referred to as Ra12-P501S-F) was confirmed by DNA sequencing.

The fusion construct was transformed into BL21(DE3)pLysE, pLysS and CodonPlus *E. coli* (Stratagene) and grown overnight in LB broth with kanamycin. The  
5 resulting culture was induced with IPTG. Protein was transferred to PVDF membrane and blocked with 5% non-fat milk (in PBS-Tween buffer), washed three times and incubated with mouse anti-His tag antibody (Clontech) for 1 hour. The membrane was washed 3 times and probed with HRP-Protein A (Zymed) for 30 min. Finally, the membrane was washed 3 times and developed with ECL (Amersham). No expression  
10 was detected by Western blot. Similarly, no expression was detected by Western blot when the Ra12-P501S-F fusion was used for expression in BL21CodonPlus by CE6 phage (Invitrogen).

An N-terminal fragment of P501S (amino acids 36-325 of SEQ ID NO: 113) was cloned down-stream of the first 30 amino acids of the *M. tuberculosis* antigen  
15 Ra12 in pET17b as follows. P501S DNA was used to perform PCR using the primers AW025 (SEQ ID NO: 485) and AW027 (SEQ ID NO: 487). AW027 is an antisense cloning primer that contains an EcoRI site and a stop codon. DNA amplification was performed essentially as described above. The resulting PCR product was cloned to Ra12 in pET17b at the HindIII and EcoRI sites. The fusion construct (referred to as  
20 Ra12-P501S-N) was confirmed by DNA sequencing.

The Ra12-P501S-N fusion construct was used for expression in BL21(DE3)pLysE, pLysS and CodonPlus, essentially as described above. Using Western blot analysis, protein bands were observed at the expected molecular weight of 36 kDa. Some high molecular weight bands were also observed, probably due to  
25 aggregation of the recombinant protein. No expression was detected by Western blot when the Ra12-P501S-F fusion was used for expression in BL21CodonPlus by CE6 phage.

A fusion construct comprising a C-terminal portion of P501S (amino acids 257-553 of SEQ ID NO: 113) located down-stream of the first 30 amino acids of  
30 the *M. tuberculosis* antigen Ra12 (SEQ ID NO: 484) was prepared as follows. P501S

DNA was used to perform PCR using the primers AW026 (SEQ ID NO: 488) and AW003 (SEQ ID NO: 486). AW026 is a sense cloning primer that contains a HindIII site. DNA amplification was performed essentially as described above. The resulting PCR product was cloned to Ra12 in pET17b at the HindIII and EcoRI sites. The  
5 sequence for the fusion construct (referred to as Ra12-P501S-C) was confirmed.

The Ra12-P501S-C fusion construct was used for expression in BL21(DE3)pLysE, pLysS and CodonPlus, as described above. A small amount of protein was detected by Western blot, with some molecular weight aggregates also being observed. Expression was also detected by Western blot when the Ra12-P501S-C  
10 fusion was used for expression in BL21CodonPlus induced by CE6 phage.

A fusion construct comprising a fragment of P501S (amino acids 36-298 of SEQ ID NO: 113) located down-stream of the *M. tuberculosis* antigen Ra12 (SEQ ID NO: 705) was prepared as follows. P501S DNA was used to perform PCR using the primers AW042 (SEQ ID NO: 706) and AW053 (SEQ ID NO: 707). AW042 is a sense  
15 cloning primer that contains a EcoRI site. AW053 is an antisense primer with stop and Xho I sites. DNA amplification was performed essentially as described above. The resulting PCR product was cloned to Ra12 in pET17b at the EcoRI and Xho I sites. The resulting fusion construct (referred to as Ra12-P501S-E2) was expressed in B834 (DE3) pLys S *E. coli* host cells in TB media for 2 h at room temperature. Expressed protein  
20 was purified by washing the inclusion bodies and running on a Ni-NTA column. The purified protein stayed soluble in buffer containing 20 mM Tris-HCl (pH 8), 100 mM NaCl, 10 mM  $\beta$ -Me and 5% glycerol. The determined cDNA and amino acid sequences for the expressed fusion protein are provided in SEQ ID NO: 708 and 709, respectively.

25 b) Expression of P501S in Baculovirus

The Bac-to-Bac baculovirus expression system (BRL Life Technologies, Inc.) was used to express P501S protein in insect cells. Full-length P501S (SEQ ID NO: 113) was amplified by PCR and cloned into the XbaI site of the donor plasmid pFastBacI. The recombinant bacmid and baculovirus were prepared according to the

manufacturer's instructions. The recombinant baculovirus was amplified in Sf9 cells and the high titer viral stocks were utilized to infect High Five cells (Invitrogen) to make the recombinant protein. The identity of the full-length protein was confirmed by N-terminal sequencing of the recombinant protein and by Western blot analysis (Figure 7). Specifically, 0.6 million High Five cells in 6-well plates were infected with either the unrelated control virus BV/ECD\_PD (lane 2), with recombinant baculovirus for P501S at different amounts or MOIs (lanes 4-8), or were uninfected (lane 3). Cell lysates were run on SDS-PAGE under reducing conditions and analyzed by Western blot with the anti-P501S monoclonal antibody P501S-10E3-G4D3 (prepared as described below). Lane 1 is the biotinylated protein molecular weight marker (BioLabs).

The localization of recombinant P501S in the insect cells was investigated as follows. The insect cells overexpressing P501S were fractionated into fractions of nucleus, mitochondria, membrane and cytosol. Equal amounts of protein from each fraction were analyzed by Western blot with a monoclonal antibody against P501S. Due to the scheme of fractionation, both nucleus and mitochondria fractions contain some plasma membrane components. However, the membrane fraction is basically free from mitochondria and nucleus. P501S was found to be present in all fractions that contain the membrane component, suggesting that P501S may be associated with plasma membrane of the insect cells expressing the recombinant protein.

#### c) Expression of P501S in Mammalian Cells

Full-length P501S (553 amino acids; SEQ ID NO: 113) was cloned into various mammalian expression vectors, including pCEP4 (Invitrogen), pVR1012 (Vical, San Diego, CA) and a modified form of the retroviral vector pBMN, referred to as pBIB. Transfection of P501S/pCEP4 and P501S/pVR1012 into HEK293 fibroblasts was carried out using the Fugene transfection reagent (Boehringer Mannheim). Briefly, 2 ul of Fugene reagent was diluted into 100 ul of serum-free media and incubated at room temperature for 5-10 min. This mixture was added to 1 ug of P501S plasmid DNA, mixed briefly and incubated for 30 minutes at room temperature. The

Fugene/DNA mixture was added to cells and incubated for 24-48 hours. Expression of recombinant P501S in transfected HEK293 fibroblasts was detected by means of Western blot employing a monoclonal antibody to P501S.

Transfection of p501S/pCEP4 into CHO-K cells (American Type Culture Collection, Rockville, MD) was carried out using GenePorter transfection reagent (Gene Therapy Systems, San Diego, CA). Briefly, 15 µl of GenePorter was diluted in 500 µl of serum-free media and incubated at room temperature for 10 min. The GenePorter/media mixture was added to 2 µg of plasmid DNA that was diluted in 500 µl of serum-free media, mixed briefly and incubated for 30 min at room temperature. CHO-K cells were rinsed in PBS to remove serum proteins, and the GenePorter/DNA mix was added and incubated for 5 hours. The transfected cells were then fed an equal volume of 2x media and incubated for 24-48 hours.

FACS analysis of P501S transiently infected CHO-K cells, demonstrated surface expression of P501S. Expression was detected using rabbit polyclonal antisera raised against a P501S peptide, as described below. Flow cytometric analysis was performed using a FaCScan (Becton Dickinson), and the data were analyzed using the Cell Quest program.

d) Expression of P501S in *S. cerevisiae*

P501S was expressed in yeast, directed in membranes, using the yeast  $\alpha$  prepro signal sequence. The natural signal sequence and first luminal domain of P501S was deleted in order to conserve the natural positioning of the expressed P501S protein.

Specifically, the  $\alpha$  prepro signal sequence of *S. cerevisiae* linked to amino acids 55-553 of SEQ ID NO: 113 with a His tag tail was cloned into the plasmid pRIT15068 with the CUP1 promoter and transfected into *S. cerevisiae* strain Y1790. The Y1790 strain is Leu<sup>+</sup> and His<sup>-</sup>. Expression of protein was induced by addition of either 500 µM or 250 µM of CuSO<sub>4</sub> at 30 °C in minimal medium supplemented with histidine. Cells were harvested 24 hours after induction. Extracts were prepared by growing cells to a concentration of OD<sub>600</sub> 5.0 in 50 mM citrate phosphate buffer (pH 4.0) plus 130 mM NaCl supplemented with protease inhibitors. Cells were disrupted

using glass beads and centrifuged for 20 min at 15,000 g. The recombinant protein was found to be 100% pellet associated.

Expression of the recombinant protein (molecular weight 63 kD) was demonstrated by Western blot analysis, using the anti-P501S monoclonal antibody 10E-D4-G3 described below. The amino acid sequence of the expressed protein is provided in SEQ ID NO: 792.

Fermentation processes for the production of the  $\alpha$  prepro-P501S-His tag recombinant protein in *S. cerevisiae* (strain Y1790 – CUP1 inducible promoter) were evaluated as follows. One hundred  $\mu$ l of a master seed containing  $2.5 \times 10^8$  cells/ml of transformed *S. cerevisiae* Y1790 were spread on FSC004AA solid medium. The composition of the FSC004AA medium is as follows: glucose 10 g/l;  $\text{Na}_2\text{MoO}_4 \cdot 2\text{H}_2\text{O}$  0.0002 g/l; folic acid 0.000064 g/l;  $\text{KH}_2\text{PO}_4$  1 g/l;  $\text{MnSO}_4 \cdot \text{H}_2\text{O}$  0.0004 g/l; Inositol 0.064 g/l;  $\text{MgSO}_4 \cdot 7\text{H}_2\text{O}$  0.5 g/l;  $\text{H}_3\text{BO}_3$  0.0005 g/l; Pyridoxine 0.008 g/l;  $\text{CaCl}_2 \cdot 2\text{H}_2\text{O}$  0.1 g/l; KI 0.0001 g/l; Thiamine 0.008 g/l; NaCl 0.1 g/l;  $\text{CoCl}_2 \cdot 6\text{H}_2\text{O}$  0.00009 g/l; Niacin 0.000032 g/l;  $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$  0.0002 g/l; Riboflavin 0.000016 g/l; Panthotenate Ca 0.008 g/l;  $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$  0.00004 g/l; Biotin 0.000064 g/l; para-aminobenzoic acid 0.000016 g/l;  $\text{ZnSO}_4 \cdot 7\text{H}_2\text{O}$  0.0004 g/l;  $(\text{NH}_4)_2\text{SO}_4$  5 g/l; agar 18 g/l; Histidine 0.1 g/l.

Two plates were incubated for 26 h at 30 °C. These solid pre-cultures were harvested in 5 ml of liquid medium FSC007AA and 0.5 ml (or  $9.3 \times 10^7$  cells) of this suspension was used to inoculate 2 liquid pre-cultures.

The composition of the FSC007AA medium is as follows: Glucose 10 g/l;  $\text{Na}_2\text{MoO}_4 \cdot 2\text{H}_2\text{O}$  0.0002 g/l; folic acid 0.000064 g/l;  $\text{KH}_2\text{PO}_4$  1 g/l;  $\text{MnSO}_4 \cdot \text{H}_2\text{O}$  0.0004 g/l; Inositol 0.064 g/l;  $\text{MgSO}_4 \cdot 7\text{H}_2\text{O}$  0.5 g/l;  $\text{H}_3\text{BO}_3$  0.0005 g/l; Pyridoxine 0.008 g/l;  $\text{CaCl}_2 \cdot 2\text{H}_2\text{O}$  0.1 g/l; KI 0.0001 g/l; Thiamine 0.008 g/l; NaCl 0.1 g/l;  $\text{CoCl}_2 \cdot 6\text{H}_2\text{O}$  0.00009 g/l; Niacine 0.000032 g/l;  $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$  0.0002 g/l; Riboflavin 0.000016 g/l; Panthotenate Ca 0.008 g/l;  $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$  0.00004 g/l; Biotin 0.000064 g/l; para-aminobenzoic acid 0.000016 g/l;  $\text{ZnSO}_4 \cdot 7\text{H}_2\text{O}$  0.0004 g/l;  $(\text{NH}_4)_2\text{SO}_4$  5 g/l; Histidine 0.1 g/l.

These pre-cultures were run for 20 hours in 2L flasks containing 400 ml of medium FSC007AA in order to obtain an OD of 1.8. The other characteristics of these pre-cultures are as follows: pH 2.8; glucose 2.3 g/L; ethanol 3.4 g/L.



The best timing for liquid pre-cultures for strain Y1790 was determined in preliminary experiments. Liquid pre-cultures containing 400 ml of medium and inoculated with various volumes of Master Seed (0.25, 0.5, 1 or 2 ml) were monitored in order to identify the best inoculum size and timing. Glucose, ethanol, pH, OD and  
5 cell number (determined by flow cytometry) were followed between 16 and 23 hours of culture. Glucose exhaustion and maximal biomass were obtained after 20 hour incubation with 0.5 inoculum. These conditions were adopted for transferring the pre-culture into fermentation.

In total, 800ml of pre-culture were used to inoculate a 20 L fermenter  
10 containing 5L of medium FSC002AA. Three ml of irradiated antifoam were added before inoculation. The composition of the FSC002AA medium is as follows:  
(NH<sub>4</sub>)<sub>2</sub>SO<sub>4</sub> 6.4 g/l; Na<sub>2</sub>MoO<sub>4</sub>.2H<sub>2</sub>O 2.05 mg/l; folic acid 0.54 mg/l; KH<sub>2</sub>PO<sub>4</sub> 8.25 g/l;  
MnSO<sub>4</sub>.H<sub>2</sub>O 4.1 mg/l; inositol 540 mg/l; MgSO<sub>4</sub>.7H<sub>2</sub>O 4.69 g/l; H<sub>3</sub>BO<sub>3</sub> 5.17 mg/l;  
pyridoxine 68 mg/l; CaCl<sub>2</sub>.2H<sub>2</sub>O 0.92 g/l; KI 1.03 mg/l; thiamine 68 mg/l; NaCl 0.06g/l;  
15 CoCl<sub>2</sub>.6H<sub>2</sub>O 0.92 mg/l; Niacine 0.27 mg/l; HCl 1 ml/l; FeCl<sub>3</sub>.6H<sub>2</sub>O 9.92 mg/l;  
Riboflavin 0.13 mg/l; CuSO<sub>4</sub>.5H<sub>2</sub>O 0.41 mg/l; Glucose 0.14 g/l; Panthotenate Ca 68  
mg/l; ZnSO<sub>4</sub>.7H<sub>2</sub>O 4.1 mg/l; Biotin 0.54 mg/l; para-aminobenzoic acid 0.13 mg/l;  
Histidine 0.3 g/l

The carbon source (glucose) was supplemented by a continuous feeding  
20 of FFB004AA medium. The composition of the FFB004AA medium is as follows:  
glucose 350 g/l; Na<sub>2</sub>MoO<sub>4</sub>.2H<sub>2</sub>O 5.15 mg/l; folic acid 1.36 mg/l; KH<sub>2</sub>PO<sub>4</sub> 20.6 g/l;  
MnSO<sub>4</sub>.H<sub>2</sub>O 10.3 mg/l; inositol 1350 mg/l; MgSO<sub>4</sub>.7H<sub>2</sub>O 11.7 g/l; H<sub>3</sub>BO<sub>3</sub> 12.9 mg/l;  
pyridoxine 170 mg/l; CaCl<sub>2</sub>.2H<sub>2</sub>O 2.35 g/l; KI 2.6 mg/l; thiamine 170 mg/l; NaCl 0.15 g/l;  
CoCl<sub>2</sub>.6H<sub>2</sub>O 2.3 mg/l; niacine 0.67 mg/l; HCl 2.5 ml/l; FeCl<sub>3</sub>.6H<sub>2</sub>O 24.8 mg/l;  
25 riboflavin; 0.33 mg/l; CuSO<sub>4</sub>.5H<sub>2</sub>O 1.03 mg/l; biotin 1.36 mg/l; panthotenate Ca 170  
mg/l; ZnSO<sub>4</sub>.7H<sub>2</sub>O 10.3 mg/l; para-aminobenzoic acid: 0.33 mg/l; histidine 5.35 g/l.

The residual glucose concentration was maintained very low ( $\leq$ 50 mg/L) in order to minimize ethanol production by fermentation. This was achieved by limiting the development of the microorganism using a limited glucose feed rate. The Standard  
30 biomass content (OD 80-90) was reached in fermentation after 44 hour growth phase.

CUP1 promoter was then induced by adding 500 $\mu$ M CuSO<sub>4</sub> in order to

produce P501S antigen.  $\text{CuSO}_4$  addition was followed by ethanol accumulation (up to 6 g/L), and the glucose feeding rate was then reduced in order to consume the ethanol. The copper available for the microorganism was monitored by testing Cu ion concentration in the broth supernatant using a spectrophotometric copper assay (DETC  
5 method). The fermentation was then supplemented by  $\text{CuSO}_4$  throughout the induction phase in order to maintain its concentration between 150 and 250  $\mu\text{M}$  in the supernatant. The biomass reached an OD of 100 at the end of induction. Cells were harvested after 8 hours of induction.

Cell homogenate was prepared and analysed by SDS-PAGE and Western  
10 Blot using standard protocols. A major protein band with the expected molecular weight of 62KD was detected by Western blot using anti-P501S monoclonal antibodies. Western blot analysis also showed that the major 62KD band was progressively produced from 30 minutes of induction on, and reached a maximum after 3 hours. No more antigen seemed to be produced between 3 and 12 hours of induction.

15 The number of passages through a French Press necessary to extract all the antigen from the cells was evaluated. One, three and five passages were tested and total cell lysates, supernatants and pellets of cell lysates were analysed by Western blot. Three passages through a French Press were sufficient to completely extract the antigen. The antigen was present in the insoluble fraction.

20

#### e) Expression of P703P in Baculovirus

The cDNA for full-length P703P-DE5 (SEQ ID NO: 326), together with several flanking restriction sites, was obtained by digesting the plasmid pCDNA703 with restriction endonucleases Xba I and Hind III. The resulting restriction fragment  
25 (approx. 800 base pairs) was ligated into the transfer plasmid pFastBacI which was digested with the same restriction enzymes. The sequence of the insert was confirmed by DNA sequencing. The recombinant transfer plasmid pFBP703 was used to make recombinant bacmid DNA and baculovirus using the Bac-To-Bac Baculovirus expression system (BRL Life Technologies). High Five cells were infected with the  
30 recombinant virus BVP703, as described above, to obtain recombinant P703P protein.

e) Expression of P788P in *E. Coli*

A truncated, N-terminal portion, of P788P (residues 1-644 of SEQ ID NO: 777; referred to as P788P-N) fused with a C-terminal 6xHis Tag was expressed in *E. coli* as follows. P788P cDNA was amplified using the primers AW080 and AW081 (SEQ ID NO: 672 and 673). AW080 is a sense cloning primer with an NdeI site. AW081 is an antisense cloning primer with a XhoI site. The PCR-amplified P788P, as well as the vector pCRX1, were digested with NdeI and XhoI. Vector and insert were ligated and transformed into NovaBlue cells. Colonies were randomly screened for insert and then sequenced. P788P-N clone #6 was confirmed to be identical to the designed construct. The expression construct P788P-N #6/pCRX1 was transformed into *E. coli* BL21 CodonPlus-RIL competent cells. After induction, most of the cells grew well, achieving OD600 of greater than 2.0 after 3 hr. Coomassie stained SDS-PAGE showed an over-expressed band at about 75 kD. Western blot analysis using a 6xHisTag antibody confirmed the band was P788P-N. The determined cDNA sequence for P788P-N is provided in SEQ ID NO: 674, with the corresponding amino acid sequence being provided in SEQ ID NO: 675.

f) Expression of P510S in *E. Coli*

The P510S protein has 9 potential transmembrane domains and is predicted to be located at the plasma membrane. The C-terminal protein of this protein, as well as the predicted third extracellular domain of P510S were expressed in *E. coli* as follows.

The expression construct referred to as Ra12-P501S-C was designed to have a 6 HisTag at the N-terminal end, followed by the *M. tuberculosis* antigen Ra12 (SEQ ID NO: 676) and then the C-terminal portion of P510S (amino residues 1176-1261 of SEQ ID NO: 538). Full-length P510S was used to amplify the P510S-C fragment by PCR using the primers AW056 and AW057 (SEQ ID NO: 677 and 678, respectively). AW056 is a sense cloning primer with an EcoRI site. AW057 is an antisense primer with stop and XhoI sites. The amplified P501S fragment and Ra12/pCRX1 were digested with EcoRI and XhoI and then purified. The insert and

vector were ligated together and transformed into NovaBlue. Colonies were randomly screened for insert and sequences. For protein expression, the expression construct was transformed into *E. coli* BL21 (DE3) CodonPlus-RIL competent cells. A mini-induction screen was performed to optimize the expression conditions. After induction  
5 the cells grew well, achieving OD 600 nm greater than 2.0 after 3 hours. Coomassie stain SDS-PAGE showed a highly over-expressed band at approx. 30 kD. Though this is higher than the expected molecular weight, western blot analysis was positive, showing this band to be the His tag-containing protein. The optimized culture conditions are as follows. Dilute overnight culture/daytime culture (LB + kanamycin +  
10 chloramphenicol) into 2xYT (with kanamycin and chloramphenicol) at a ratio of 25 ml culture to 1 liter 2xYT. Allow to grow at 37 °C until OD600 = 0.6. Take an aliquot out as T0 sample. Add 1 mM IPTG and allow to grow at 30 °C for 3 hours. Take out a T3 sample, spin down cells and store at -80 °C. The determined cDNA and amino acid sequences for the Ra12-P510S-C construct are provided in SEQ ID NO: 679 and 682,  
15 respectively.

The expression construct P510S-C was designed to have a 5' added start codon and a glycine (GGA) codon and then the P510S C terminal fragment followed by the in frame 6x histidine tag and stop codon from the pET28b vector. The cloning strategy is similar to that used for Ra12-P510S-C, except that the PCR primers employed were  
20 those shown in SEQ ID NO: 685 and 686, respectively and the NcoI/XhoI cut in pET28b was used. The primer of SEQ ID NO: 685 created a 5' NcoI site and added a start codon. The antisense primer of SEQ ID NO: 686 creates a XhoI site on P510S C terminal fragment. Clones were confirmed by sequencing. For protein expression, the expression construct was transformed into *E. coli* BL21 (DE3) CodonPlus-RIL  
25 competent cells. An OD600 of greater than 2.0 was obtained 30 hours after induction. Coomassie stained SDS-PAGE showed an over-expressed band at about 11 kD. Western blot analysis confirmed that the band was P510S-C, as did N-terminal protein sequencing. The optimized culture conditions are as follows: dilute overnight culture/daytime culture (LB + kanamycin + chloramphenicol) into 2x YT (+ kanamycin  
30 and chloramphenicol) at a ratio of 25 mL culture to 1 liter 2x YT, and allow to grow at

37 °C until an OD 600 of about 0.5 is reached. Take out an aliquot as T0 sample. Add 1 mM IPTG and allow to grow at 30 °C for 3 hours. Spin down the cells and store at -80 °C until purification. The determined cDNA and amino acid sequences for the P510S-C construct are shown in SEQ ID NO: 680 and 683, respectively.

5           The predicted third extracellular domain of P510S (P510S-E3; residues 328-676 of SEQ ID NO: 538) was expressed in *E. coli* as follows. The P510S fragment was amplified by PCR using the primers shown in SEQ ID NO: 687 and 688. The primer of SEQ ID NO: 687 is a sense primer with an NdeI site for use in ligating into pPDM. The primer of SEQ ID NO: 688 is an antisense primer with an added XhoI site  
10 for use in ligating into pPDM. The resulting fragment was cloned to pPDM at the NdeI and XhoI sites. Clones were confirmed by sequencing. For protein expression, the clone was transformed into *E. coli* BL21 (DE3) CodonPlus-RIL competent cells. After induction, an OD600 of greater than 2.0 was achieved after 3 hours. Coomassie stained SDS-PAGE showed an over-expressed band at about 39 kD, and N-terminal sequencing  
15 confirmed the N-terminal to be that of P510S-E3. Optimized culture conditions are as follows: dilute overnight culture/daytime culture (LB + kanamycin + chloramphenicol) into 2x YT (kanamycin and chloramphenicol) at a ratio of 25 ml culture to 1 liter 2x YT. Allow to grow at 37 °C until OD 600 equals 0.6. Take out an aliquot as T0 sample. Add 1 mM IPTG and allow to grow at 30 °C for 3 hours. Take out a T3  
20 sample, spin down the cells and store at -80 °C until purification. The determined cDNA and amino acid sequences for the P501S-E3 construct are provided in SEQ ID NO: 681 and 684, respectively.

g) Expression of P775S in *E. Coli*

25           The antigen P775P contains multiple open reading frames (ORF). The third ORF, encoding the protein of SEQ ID NO: 483, has the best motif score. An expression fusion construct containing the *M. tuberculosis* antigen Ra12 (SEQ ID NO: 676) and P775P-ORF3 with an N-terminal 6x HisTag was prepared as follows. P775P-ORF3 was amplified using the sense PCR primers of SEQ ID NO: 689 and the anti-sense PCR primer of SEQ ID NO: 690. The PCR amplified fragment of P775P and

Ra12/pCRX1 were digested with the restriction enzymes EcoRI and XhoI. Vector and insert were ligated and then transformed into NovaBlue cells. Colonies were randomly screened for insert and then sequenced. A clone having the desired sequence was transformed into *E. coli* BL21 (DE3) CodonPlus-RIL competent cells. Two hours after induction, the cell density peaked at OD600 of approximately 1.8. Coomassie stained SDS-PAGE showed an over-expressed band at about 31 kD. Western blot using 6x HisTag antibody confirmed that the band was Ra12-P775P-ORF3. The determined cDNA and amino acid sequences for the fusion construct are provided in SEQ ID NO: 691 and 692, respectively.

10

#### **H) EXPRESSION OF A P703P HIS TAG FUSION PROTEIN IN E. COLI**

The cDNA for the coding region of P703P was prepared by PCR using the primers of SEQ ID NO: 693 and 694. The PCR product was digested with EcoRI restriction enzyme, gel purified and cloned into a modified pET28 vector with a His tag in frame, which had been digested with Eco72I and EcoRI restriction enzymes. The correct construct was confirmed by DNA sequence analysis and then transformed into *E. coli* BL21 (DE3) pLys S expression host cells. The determined amino acid and cDNA sequences for the expressed recombinant P703P are provided in SEQ ID NO: 695 and 696, respectively.

20

#### **I) EXPRESSION OF A P705P HIS TAG FUSION PROTEIN IN E. COLI**

The cDNA for the coding region of P705P was prepared by PCR using the primers of SEQ ID NO: 697 and 698. The PCR product was digested with EcoRI restriction enzyme, gel purified and cloned into a modified pET28 vector with a His tag in frame, which had been digested with Eco72I and EcoRI restriction enzymes. The correct construct was confirmed by DNA sequence analysis and then transformed into *E. coli* BL21 (DE3) pLys S and BL21 (DE3) CodonPlus expression host cells. The determined amino acid and cDNA sequences for the expressed recombinant P705P are provided in SEQ ID NO: 699 and 700, respectively.

30

#### J) EXPRESSION OF A P711P HIS TAG FUSION PROTEIN IN *E. COLI*

The cDNA for the coding region of P711P was prepared by PCR using the primers of SEQ ID NO: 701 and 702. The PCR product was digested with EcoRI restriction enzyme, gel purified and cloned into a modified pET28 vector with a His tag in frame, which had been digested with Eco72I and EcoRI restriction enzymes. The correct construct was confirmed by DNA sequence analysis and then transformed into *E. coli* BL21 (DE3) pLys S and BL21 (DE3) CodonPlus expression host cells. The determined amino acid and cDNA sequences for the expressed recombinant P711P are provided in SEQ ID NO: 703 and 704, respectively.

#### EXAMPLE 18

##### PREPARATION AND CHARACTERIZATION OF ANTIBODIES AGAINST PROSTATE-SPECIFIC POLYPEPTIDES

##### a) Preparation and Characterization of Polyclonal Antibodies against P703P, P504S and P509S

Polyclonal antibodies against P703P, P504S and P509S were prepared as follows.

Each prostate tumor antigen expressed in an *E. coli* recombinant expression system was grown overnight in LB broth with the appropriate antibiotics at 37°C in a shaking incubator. The next morning, 10 ml of the overnight culture was added to 500 ml of 2x YT plus appropriate antibiotics in a 2L-baffled Erlenmeyer flask. When the Optical Density (at 560 nm) of the culture reached 0.4-0.6, the cells were induced with IPTG (1 mM). Four hours after induction with IPTG, the cells were harvested by centrifugation. The cells were then washed with phosphate buffered saline and centrifuged again. The supernatant was discarded and the cells were either frozen for future use or immediately processed. Twenty ml of lysis buffer was added to the cell pellets and vortexed. To break open the *E. coli* cells, this mixture was then run

through the French Press at a pressure of 16,000 psi. The cells were then centrifuged again and the supernatant and pellet were checked by SDS-PAGE for the partitioning of the recombinant protein. For proteins that localized to the cell pellet, the pellet was resuspended in 10 mM Tris pH 8.0, 1% CHAPS and the inclusion body pellet was washed and centrifuged again. This procedure was repeated twice more. The washed inclusion body pellet was solubilized with either 8 M urea or 6 M guanidine HCl containing 10 mM Tris pH 8.0 plus 10 mM imidazole. The solubilized protein was added to 5 ml of nickel-chelate resin (Qiagen) and incubated for 45 min to 1 hour at room temperature with continuous agitation. After incubation, the resin and protein mixture were poured through a disposable column and the flow through was collected. The column was then washed with 10-20 column volumes of the solubilization buffer. The antigen was then eluted from the column using 8M urea, 10 mM Tris pH 8.0 and 300 mM imidazole and collected in 3 ml fractions. A SDS-PAGE gel was run to determine which fractions to pool for further purification.

As a final purification step, a strong anion exchange resin such as HiPrepQ (Biorad) was equilibrated with the appropriate buffer and the pooled fractions from above were loaded onto the column. Each antigen was eluted off the column with a increasing salt gradient. Fractions were collected as the column was run and another SDS-PAGE gel was run to determine which fractions from the column to pool. The pooled fractions were dialyzed against 10 mM Tris pH 8.0. The proteins were then vialled after filtration through a 0.22 micron filter and the antigens were frozen until needed for immunization.

Four hundred micrograms of each prostate antigen was combined with 100 micrograms of muramyldipeptide (MDP). Every four weeks rabbits were boosted with 100 micrograms mixed with an equal volume of Incomplete Freund's Adjuvant (IFA). Seven days following each boost, the animal was bled. Sera was generated by incubating the blood at 4°C for 12-4 hours followed by centrifugation.

Ninety-six well plates were coated with antigen by incubating with 50 microliters (typically 1 microgram) of recombinant protein at 4 °C for 20 hours. 250 microliters of BSA blocking buffer was added to the wells and incubated at room



temperature for 2 hours. Plates were washed 6 times with PBS/0.01% Tween. Rabbit sera was diluted in PBS. Fifty microliters of diluted sera was added to each well and incubated at room temperature for 30 min. Plates were washed as described above before 50 microliters of goat anti-rabbit horse radish peroxidase (HRP) at a 1:10000  
5 dilution was added and incubated at room temperature for 30 min. Plates were again washed as described above and 100 microliters of TMB microwell peroxidase substrate was added to each well. Following a 15 min incubation in the dark at room temperature, the colorimetric reaction was stopped with 100 microliters of 1N H<sub>2</sub>SO<sub>4</sub> and read immediately at 450 nm. All polyclonal antibodies showed immunoreactivity  
10 to the appropriate antigen.

b) Preparation and Characterization of Antibodies against P501S

A murine monoclonal antibody directed against the carboxy-terminus of the prostate-specific antigen P501S was prepared as follows.

A truncated fragment of P501S (amino acids 355-526 of SEQ ID NO:  
15 113) was generated and cloned into the pET28b vector (Novagen) and expressed in *E. coli* as a thioredoxin fusion protein with a histidine tag. The trx-P501S fusion protein was purified by nickel chromatography, digested with thrombin to remove the trx fragment and further purified by an acid precipitation procedure followed by reverse phase HPLC.

20 Mice were immunized with truncated P501S protein. Serum bleeds from mice that potentially contained anti-P501S polyclonal sera were tested for P501S-specific reactivity using ELISA assays with purified P501S and trx-P501S proteins. Serum bleeds that appeared to react specifically with P501S were then screened for P501S reactivity by Western analysis. Mice that contained a P501S-specific antibody  
25 component were sacrificed and spleen cells were used to generate anti-P501S antibody producing hybridomas using standard techniques. Hybridoma supernatants were tested for P501S-specific reactivity initially by ELISA, and subsequently by FACS analysis of reactivity with P501S transduced cells. Based on these results, a monoclonal hybridoma referred to as 10E3 was chosen for further subcloning. A number of subclones were

generated, tested for specific reactivity to P501S using ELISA and typed for IgG isotype. The results of this analysis are shown below in Table V. Of the 16 subclones tested, the monoclonal antibody 10E3-G4-D3 was selected for further study.

5

Table V

Isotype analysis of murine anti-P501S monoclonal antibodies

Hybridoma clone	Isotype	Estimated [Ig] in supernatant (µg/ml)
4D11	IgG1	14.6
1G1	IgG1	0.6
4F6	IgG1	72
4H5	IgG1	13.8
4H5-E12	IgG1	10.7
4H5-EH2	IgG1	9.2
4H5-H2-A10	IgG1	10
4H5-H2-A3	IgG1	12.8
4H5-H2-A10-G6	IgG1	13.6
4H5-H2-B11	IgG1	12.3
10E3	IgG2a	3.4
10E3-D4	IgG2a	3.8
10E3-D4-G3	IgG2a	9.5
10E3-D4-G6	IgG2a	10.4
10E3-E7	IgG2a	6.5
8H12	IgG2a	0.6

The specificity of 10E3-G4-D3 for P501S was examined by FACS analysis. Specifically, cells were fixed (2% formaldehyde, 10 minutes), permeabilized (0.1% saponin, 10 minutes) and stained with 10E3-G4-D3 at 0.5 – 1 µg/ml, followed by incubation with a secondary, FITC-conjugated goat anti-mouse Ig antibody (Pharmingen, San Diego, CA). Cells were then analyzed for FITC fluorescence using an Excalibur fluorescence activated cell sorter. For FACS analysis of transduced cells, B-LCL were retrovirally transduced with P501S. For analysis of infected cells, B-LCL were infected with a vaccinia vector that expresses P501S. To demonstrate specificity in these assays, B-LCL transduced with a different antigen (P703P) and uninfected B-LCL vectors were utilized. 10E3-G4-D3 was shown to bind with P501S-transduced B-

LCL and also with P501S-infected B-LCL, but not with either uninfected cells or P703P-transduced cells.

To determine whether the epitope recognized by 10E3-G4-D3 was found on the surface or in an intracellular compartment of cells, B-LCL were transduced with  
5 P501S or HLA-B8 as a control antigen and either fixed and permeabilized as described above or directly stained with 10E3-G4-D3 and analyzed as above. Specific recognition of P501S by 10E3-G4-D3 was found to require permeabilization, suggesting that the epitope recognized by this antibody is intracellular.

The reactivity of 10E3-G4-D3 with the three prostate tumor cell lines  
10 Lncap, PC-3 and DU-145, which are known to express high, medium and very low levels of P501S, respectively, was examined by permeabilizing the cells and treating them as described above. Higher reactivity of 10E3-G4-D3 was seen with Lncap than with PC-3, which in turn showed higher reactivity than DU-145. These results are in agreement with the real time PCR and demonstrate that the antibody specifically  
15 recognizes P501S in these tumor cell lines and that the epitope recognized in prostate tumor cell lines is also intracellular.

Specificity of 10E3-G4-D3 for P501S was also demonstrated by Western blot analysis. Lysates from the prostate tumor cell lines Lncap, DU-145 and PC-3, from P501S-transiently transfected HEK293 cells, and from non-transfected HEK293 cells  
20 were generated. Western blot analysis of these lysates with 10E3-G4-D3 revealed a 46 kDa immunoreactive band in Lncap, PC-3 and P501S-transfected HEK cells, but not in DU-145 cells or non-transfected HEK293 cells. P501S mRNA expression is consistent with these results since semi-quantitative PCR analysis revealed that P501S mRNA is expressed in Lncap, to a lesser but detectable level in PC-3 and not at all in DU-145  
25 cells. Bacterially expressed and purified recombinant P501S (referred to as P501SStr2) was recognized by 10E3-G4-D3 (24 kDa), as was full-length P501S that was transiently expressed in HEK293 cells using either the expression vector VR1012 or pCEP4. Although the predicted molecular weight of P501S is 60.5 kDa, both transfected and "native" P501S run at a slightly lower mobility due to its hydrophobic nature.

Immunohistochemical analysis was performed on prostate tumor and a panel of normal tissue sections (prostate, adrenal, breast, cervix, colon, duodenum, gall bladder, ileum, kidney, ovary, pancreas, parotid gland, skeletal muscle, spleen and testis). Tissue samples were fixed in formalin solution for 24 hours and embedded in paraffin before being sliced into 10 micron sections. Tissue sections were permeabilized and incubated with 10E3-G4-D3 antibody for 1 hr. HRP-labeled anti-mouse followed by incubation with DAB chromogen was used to visualize P501S immunoreactivity. P501S was found to be highly expressed in both normal prostate and prostate tumor tissue but was not detected in any of the other tissues tested.

To identify the epitope recognized by 10E3-G4-D3, an epitope mapping approach was pursued. A series of 13 overlapping 20-21 mers (5 amino acid overlap; SEQ ID NO: 489-501) was synthesized that spanned the fragment of P501S used to generate 10E3-G4-D3. Flat bottom 96 well microtiter plates were coated with either the peptides or the P501S fragment used to immunize mice, at 1 microgram/ml for 2 hours at 37 °C. Wells were then aspirated and blocked with phosphate buffered saline containing 1% (w/v) BSA for 2 hours at room temperature, and subsequently washed in PBS containing 0.1% Tween 20 (PBST). Purified antibody 10E3-G4-D3 was added at 2 fold dilutions (1000 ng – 16 ng) in PBST and incubated for 30 minutes at room temperature. This was followed by washing 6 times with PBST and subsequently incubating with HRP-conjugated donkey anti-mouse IgG (H+L) Affinipure F(ab') fragment (Jackson ImmunoResearch, West Grove, PA) at 1:20000 for 30 minutes. Plates were then washed and incubated for 15 minutes in tetramethyl benzidine. Reactions were stopped by the addition of 1N sulfuric acid and plates were read at 450 nm using an ELISA plate reader. As shown in Fig. 8, reactivity was seen with the peptide of SEQ ID NO: 496 (corresponding to amino acids 439-459 of P501S) and with the P501S fragment but not with the remaining peptides, demonstrating that the epitope recognized by 10E3-G4-D3 is localized to amino acids 439-459 of SEQ ID NO: 113.

In order to further evaluate the tissue specificity of P501S, multi-array immunohistochemical analysis was performed on approximately 4700 different human tissues encompassing all the major normal organs as well as neoplasias derived from

these tissues. Sixty-five of these human tissue samples were of prostate origin. Tissue sections 0.6 mm in diameter were formalin-fixed and paraffin embedded. Samples were pretreated with HIER using 10 mM citrate buffer pH 6.0 and boiling for 10 min. Sections were stained with 10E3-G4-D3 and P501S immunoreactivity was visualized with HRP. All the 65 prostate tissues samples (5 normal, 55 untreated prostate tumors, 5 hormone refractory prostate tumors) were positive, showing distinct perinuclear staining. All other tissues examined were negative for P501S expression.

c) Preparation and Characterization of Antibodies against P503S

A fragment of P503S (amino acids 113-241 of SEQ ID NO: 114) was expressed and purified from bacteria essentially as described above for P501S and used to immunize both rabbits and mice. Mouse monoclonal antibodies were isolated using standard hybridoma technology as described above. Rabbit monoclonal antibodies were isolated using Selected Lymphocyte Antibody Method (SLAM) technology at Immgenics Pharmaceuticals (Vancouver, BC, Canada). Table VI, below, lists the monoclonal antibodies that were developed against P503S.

Table VI

Antibody	Species
20D4	Rabbit
JA1	Rabbit
1A4	Mouse
1C3	Mouse
1C9	Mouse
1D12	Mouse
2A11	Mouse
2H9	Mouse
4H7	Mouse
8A8	Mouse
8D10	Mouse
9C12	Mouse
6D12	Mouse

The DNA sequences encoding the complementarity determining regions (CDRs) for the rabbit monoclonal antibodies 20D4 and JA1 were determined and are provided in SEQ ID NO: 502 and 503, respectively.

5           In order to better define the epitope binding region of each of the antibodies, a series of overlapping peptides were generated that span amino acids 109-213 of SEQ ID NO: 114. These peptides were used to epitope map the anti-P503S monoclonal antibodies by ELISA as follows. The recombinant fragment of P503S that was employed as the immunogen was used as a positive control. Ninety-six well  
10   microtiter plates were coated with either peptide or recombinant antigen at 20 ng/well overnight at 4 °C. Plates were aspirated and blocked with phosphate buffered saline containing 1% (w/v) BSA for 2 hours at room temperature then washed in PBS containing 0.1% Tween 20 (PBST). Purified rabbit monoclonal antibodies diluted in PBST were added to the wells and incubated for 30 min at room temperature. This was  
15   followed by washing 6 times with PBST and incubation with Protein-A HRP conjugate at a 1:2000 dilution for a further 30 min. Plates were washed six times in PBST and incubated with tetramethylbenzidine (TMB) substrate for a further 15 min. The reaction was stopped by the addition of 1N sulfuric acid and plates were read at 450 nm using at ELISA plate reader. ELISA with the mouse monoclonal antibodies was performed with  
20   supernatants from tissue culture run neat in the assay.

All of the antibodies bound to the recombinant P503S fragment, with the exception of the negative control SP2 supernatant. 20D4, JA1 and 1D12 bound strictly to peptide #2101 (SEQ ID NO: 504), which corresponds to amino acids 151-169 of SEQ ID NO: 114. 1C3 bound to peptide #2102 (SEQ ID NO: 505), which corresponds  
25   to amino acids 165-184 of SEQ ID NO: 114. 9C12 bound to peptide #2099 (SEQ ID NO: 522), which corresponds to amino acids 120-139 of SEQ ID NO: 114. The other antibodies bind to regions that were not examined in these studies.

Subsequent to epitope mapping, the antibodies were tested by FACS analysis on a cell line that stably expressed P503S to confirm that the antibodies bind to  
30   cell surface epitopes. Cells stably transfected with a control plasmid were employed as

a negative control. Cells were stained live with no fixative. 0.5 ug of anti-P503S monoclonal antibody was added and cells were incubated on ice for 30 min before being washed twice and incubated with a FITC-labelled goat anti-rabbit or mouse secondary antibody for 20 min. After being washed twice, cells were analyzed with an Excalibur  
5 fluorescent activated cell sorter. The monoclonal antibodies 1C3, 1D12, 9C12, 20D4 and JA1, but not 8D3, were found to bind to a cell surface epitope of P503S.

In order to determine which tissues express P503S, immunohistochemical analysis was performed, essentially as described above, on a panel of normal tissues (prostate, adrenal, breast, cervix, colon, duodenum, gall bladder,  
10 ileum, kidney, ovary, pancreas, parotid gland, skeletal muscle, spleen and testis). HRP-labeled anti-mouse or anti-rabbit antibody followed by incubation with TMB was used to visualize P503S immunoreactivity. P503S was found to be highly expressed in prostate tissue, with lower levels of expression being observed in cervix, colon, ileum and kidney, and no expression being observed in adrenal, breast, duodenum, gall  
15 bladder, ovary, pancreas, parotid gland, skeletal muscle, spleen and testis.

Western blot analysis was used to characterize anti-P503S monoclonal antibody specificity. SDS-PAGE was performed on recombinant (rec) P503S expressed in and purified from bacteria and on lysates from HEK293 cells transfected with full length P503S. Protein was transferred to nitrocellulose and then Western blotted with  
20 each of the anti-P503S monoclonal antibodies (20D4, JA1, 1D12, 6D12 and 9C12) at an antibody concentration of 1 ug/ml. Protein was detected using horse radish peroxidase (HRP) conjugated to either a goat anti-mouse monoclonal antibody or to protein A-sepharose. The monoclonal antibody 20D4 detected the appropriate molecular weight 14 kDa recombinant P503S (amino acids 113-241) and the 23.5 kDa  
25 species in the HEK293 cell lysates transfected with full length P503S. Other anti-P503S monoclonal antibodies displayed similar specificity by Western blot.

#### d) Preparation and Characterization of Antibodies against P703P

Rabbits were immunized with either a truncated (P703Ptr1; SEQ ID NO: 172) or full-length mature form (P703Pfl; SEQ ID NO: 523) of recombinant P703P

protein was expressed in and purified from bacteria as described above. Affinity purified polyclonal antibody was generated using immunogen P703Pfl or P703Ptrl attached to a solid support. Rabbit monoclonal antibodies were isolated using SLAM technology at Immgenics Pharmaceuticals. Table VII below lists both the polyclonal and monoclonal antibodies that were generated against P703P.

Table VII

Antibody	Immunogen	Species/type
Aff. Purif. P703P (truncated); #2594	P703Ptrl	Rabbit polyclonal
Aff. Purif. P703P (full length); #9245	P703Pfl	Rabbit polyclonal
2D4	P703Ptrl	Rabbit monoclonal
8H2	P703Ptrl	Rabbit monoclonal
7H8	P703Ptrl	Rabbit monoclonal

The DNA sequences encoding the complementarity determining regions (CDRs) for the rabbit monoclonal antibodies 8H2, 7H8 and 2D4 were determined and are provided in SEQ ID NO: 506-508, respectively.

Epitope mapping studies were performed as described above. Monoclonal antibodies 2D4 and 7H8 were found to specifically bind to the peptides of SEQ ID NO: 509 (corresponding to amino acids 145-159 of SEQ ID NO: 172) and SEQ ID NO: 510 (corresponding to amino acids 11-25 of SEQ ID NO: 172), respectively. The polyclonal antibody 2594 was found to bind to the peptides of SEQ ID NO: 511-514, with the polyclonal antibody 9427 binding to the peptides of SEQ ID NO: 515-517.

The specificity of the anti-P703P antibodies was determined by Western blot analysis as follows. SDS-PAGE was performed on (1) bacterially expressed recombinant antigen; (2) lysates of HEK293 cells and Ltk<sup>-/-</sup> cells either untransfected or transfected with a plasmid expressing full length P703P; and (3) supernatant isolated from these cell cultures. Protein was transferred to nitrocellulose and then Western blotted using the anti-P703P polyclonal antibody #2594 at an antibody concentration of 1 ug/ml. Protein was detected using horse radish peroxidase (HRP) conjugated to an anti-rabbit antibody. A 35 kDa immunoreactive band could be observed with



recombinant P703P. Recombinant P703P runs at a slightly higher molecular weight since it is epitope tagged. In lysates and supernatants from cells transfected with full length P703P, a 30 kDa band corresponding to P703P was observed. To assure specificity, lysates from HEK293 cells stably transfected with a control plasmid were  
5 also tested and were negative for P703P expression. Other anti-P703P antibodies showed similar results.

Immunohistochemical studies were performed as described above, using anti-P703P monoclonal antibody. P703P was found to be expressed at high levels in normal prostate and prostate tumor tissue but was not detectable in all other tissues  
10 tested (breast tumor, lung tumor and normal kidney).

e) Preparation and Characterization of Antibodies against P504S

Full-length P504S (SEQ ID NO: 108) was expressed and purified from bacteria essentially as described above for P501S and employed to raise rabbit monoclonal antibodies using Selected Lymphocyte Antibody Method (SLAM)  
15 technology at Immgenics Pharmaceuticals (Vancouver, BC, Canada). The anti-P504S monoclonal antibody 13H4 was shown by Western blot to bind to both expressed recombinant P504S and to native P504S in tumor cells.

Immunohistochemical studies using 13H4 to assess P504S expression in various prostate tissues were performed as described above. A total of 104 cases,  
20 including 65 cases of radical prostatectomies with prostate cancer (PC), 26 cases of prostate biopsies and 13 cases of benign prostate hyperplasia (BPH), were stained with the anti-P504S monoclonal antibody 13H4. P504S showed strongly cytoplasmic granular staining in 64/65 (98.5%) of PCs in prostatectomies and 26/26 (100%) of PCs in prostatic biopsies. P504S was stained strongly and diffusely in carcinomas (4+ in  
25 91.2% of cases of PC; 3+ in 5.5%; 2+ in 2.2% and 1+ in 1.1%) and high grade prostatic intraepithelial neoplasia (4+ in all cases). The expression of P504S did not vary with Gleason score. Only 17/91 (18.7%) of cases of NP/BPH around PC and 2/13 (15.4%) of BPH cases were focally (1+, no 2+ to 4+ in all cases) and weakly positive for P504S in large glands. Expression of P504S was not found in small atrophic glands, postatrophic  
30 hyperplasia, basal cell hyperplasia and transitional cell metaplasia in either biopsies or

prostatectomies. P504S was thus found to be over-expressed in all Gleason scores of prostate cancer (98.5 to 100% of sensitivity) and exhibited only focal positivities in large normal glands in 19/104 of cases (82.3% of specificity). These findings indicate that P504S may be usefully employed for the diagnosis of prostate cancer.

5

## EXAMPLE 19

CHARACTERIZATION OF CELL SURFACE EXPRESSION AND  
CHROMOSOME LOCALIZATION OF THE PROSTATE-SPECIFIC ANTIGEN P501S

10 This example describes studies demonstrating that the prostate-specific antigen P501S is expressed on the surface of cells, together with studies to determine the probable chromosomal location of P501S.

The protein P501S (SEQ ID NO: 113) is predicted to have 11 transmembrane domains. Based on the discovery that the epitope recognized by the anti-  
15 P501S monoclonal antibody 10E3-G4-D3 (described above in Example 17) is intracellular, it was predicted that following transmembrane determinants would allow the prediction of extracellular domains of P501S. Fig. 9 is a schematic representation of the P501S protein showing the predicted location of the transmembrane domains and the intracellular epitope described in Example 17. Underlined sequence represents the  
20 predicted transmembrane domains, bold sequence represents the predicted extracellular domains, and italicized sequence represents the predicted intracellular domains. Sequence that is both bold and underlined represents sequence employed to generate polyclonal rabbit serum. The location of the transmembrane domains was predicted using HHMTOP as described by Tusnady and Simon (Principles Governing Amino  
25 Acid Composition of Integral Membrane Proteins: Applications to Topology Prediction, *J. Mol. Biol.* 283:489-506, 1998).

Based on Fig. 9, the P501S domain flanked by the transmembrane domains corresponding to amino acids 274-295 and 323-342 is predicted to be extracellular. The peptide of SEQ ID NO: 518 corresponds to amino acids 306-320 of  
30 P501S and lies in the predicted extracellular domain. The peptide of SEQ ID NO: 519,

which is identical to the peptide of SEQ ID NO: 518 with the exception of the substitution of the histidine with an asparagine, was synthesized as described above. A Cys-Gly was added to the C-terminus of the peptide to facilitate conjugation to the carrier protein. Cleavage of the peptide from the solid support was carried out using the  
5 following cleavage mixture: trifluoroacetic acid:ethanediol:thioanisole:water:phenol (40:1:2:2:3). After cleaving for two hours, the peptide was precipitated in cold ether. The peptide pellet was then dissolved in 10% v/v acetic acid and lyophilized prior to purification by C18 reverse phase hplc. A gradient of 5-60% acetonitrile (containing 0.05% TFA) in water (containing 0.05% TFA) was used to elute the peptide. The purity  
10 of the peptide was verified by hplc and mass spectrometry, and was determined to be >95%. The purified peptide was used to generate rabbit polyclonal antisera as described above.

Surface expression of P501S was examined by FACS analysis. Cells were stained with the polyclonal anti-P501S peptide serum at 10 µg/ml, washed,  
15 incubated with a secondary FITC-conjugated goat anti-rabbit Ig antibody (ICN), washed and analyzed for FITC fluorescence using an Excalibur fluorescence activated cell sorter. For FACS analysis of transduced cells, B-LCL were retrovirally transduced with P501S. To demonstrate specificity in these assays, B-LCL transduced with an irrelevant antigen (P703P) or nontransduced were stained in parallel. For FACS analysis of  
20 prostate tumor cell lines, Lncap, PC-3 and DU-145 were utilized. Prostate tumor cell lines were dissociated from tissue culture plates using cell dissociation medium and stained as above. All samples were treated with propidium iodide (PI) prior to FACS analysis, and data was obtained from PI-excluding (*i.e.*, intact and non-permeabilized) cells. The rabbit polyclonal serum generated against the peptide of SEQ ID NO: 519  
25 was shown to specifically recognize the surface of cells transduced to express P501S, demonstrating that the epitope recognized by the polyclonal serum is extracellular.

To determine biochemically if P501S is expressed on the cell surface, peripheral membranes from Lncap cells were isolated and subjected to Western blot analysis. Specifically, Lncap cells were lysed using a dounce homogenizer in 5 ml of  
30 homogenization buffer (250 mM sucrose, 10 mM HEPES, 1mM EDTA, pH 8.0, 1

complete protease inhibitor tablet (Boehringer Mannheim)). Lysate samples were spun at 1000 g for 5 min at 4 °C. The supernatant was then spun at 8000g for 10 min at 4 °C. Supernatant from the 8000g spin was recovered and subjected to a 100,000g spin for 30 min at 4 °C to recover peripheral membrane. Samples were then separated by SDS-  
5 PAGE and Western blotted with the mouse monoclonal antibody 10E3-G4-D3 (described above in Example 17) using conditions described above. Recombinant purified P501S, as well as HEK293 cells transfected with and over-expressing P501S were included as positive controls for P501S detection. LCL cell lysate was included as a negative control. P501S could be detected in Lncap total cell lysate, the 8000g  
10 (internal membrane) fraction and also in the 100,000g (plasma membrane) fraction. These results indicate that P501S is expressed at, and localizes to, the peripheral membrane.

To demonstrate that the rabbit polyclonal antiserum generated to the peptide of SEQ ID NO: 519 specifically recognizes this peptide as well as the  
15 corresponding native peptide of SEQ ID NO: 518, ELISA analyses were performed. For these analyses, flat-bottomed 96 well microtiter plates were coated with either the peptide of SEQ ID NO: 519, the longer peptide of SEQ ID NO: 520 that spans the entire predicted extracellular domain, the peptide of SEQ ID NO: 521 which represents the epitope recognized by the P501S-specific antibody 10E3-G4-D3, or a P501S fragment  
20 (corresponding to amino acids 355-526 of SEQ ID NO: 113) that does not include the immunizing peptide sequence, at 1 µg/ml for 2 hours at 37 °C. Wells were aspirated, blocked with phosphate buffered saline containing 1% (w/v) BSA for 2 hours at room temperature and subsequently washed in PBS containing 0.1% Tween 20 (PBST). Purified anti-P501S polyclonal rabbit serum was added at 2 fold dilutions (1000 ng -  
25 125 ng) in PBST and incubated for 30 min at room temperature. This was followed by washing 6 times with PBST and incubating with HRP-conjugated goat anti-rabbit IgG (H+L) Affinipure F(ab') fragment at 1:20000 for 30 min. Plates were then washed and incubated for 15 min in tetramethyl benzidine. Reactions were stopped by the addition of 1N sulfuric acid and plates were read at 450 nm using an ELISA plate reader. As  
30 shown in Fig. 11, the anti-P501S polyclonal rabbit serum specifically recognized the

peptide of SEQ ID NO: 519 used in the immunization as well as the longer peptide of SEQ ID NO: 520, but did not recognize the irrelevant P501S-derived peptides and fragments.

In further studies, rabbits were immunized with peptides derived from the P501S sequence and predicted to be either extracellular or intracellular, as shown in Fig. 9. Polyclonal rabbit sera were isolated and polyclonal antibodies in the serum were purified, as described above. To determine specific reactivity with P501S, FACS analysis was employed, utilizing either B-LCL transduced with P501S or the irrelevant antigen P703P, of B-LCL infected with vaccinia virus-expressing P501S. For surface expression, dead and non-intact cells were excluded from the analysis as described above. For intracellular staining, cells were fixed and permeabilized as described above. Rabbit polyclonal serum generated against the peptide of SEQ ID NO: 548, which corresponds to amino acids 181-198 of P501S, was found to recognize a surface epitope of P501S. Rabbit polyclonal serum generated against the peptide SEQ ID NO: 551, which corresponds to amino acids 543-553 of P501S, was found to recognize an epitope that was either potentially extracellular or intracellular since in different experiments intact or permeabilized cells were recognized by the polyclonal sera. Based on similar deductive reasoning, the sequences of SEQ ID NO: 541-547, 549 and 550, which correspond to amino acids 109-122, 539-553, 509-520, 37-54, 342-359, 295-323, 217-274, 143-160 and 75-88, respectively, of P501S, can be considered to be potential surface epitopes of P501S recognized by antibodies.

In further studies, mouse monoclonal antibodies were raised against amino acids 296 to 322 to P501S, which are predicted to be in an extracellular domain. A/J mice were immunized with P501S/adenovirus, followed by subsequent boosts with an *E. coli* recombinant protein, referred to as P501N, that contains amino acids 296 to 322 of P501S, and with peptide 296-322 (SEQ ID NO: 755) coupled with KLH. The mice were subsequently used for splenic B cell fusions to generate anti-peptide hybridomas. The resulting 3 clones, referred to as 4F4 (IgG1,kappa), 4G5 (IgG2a,kappa) and 9B9 (IgG1,kappa), were grown for antibody production. The mAb was purified by passing the supernatant over a Protein A-sepharose column,

followed by antibody elution using 0.2M glycine, pH 2.3. Purified antibody was neutralized by the addition of 1M Tris, pH 8, and buffer exchanged into PBS.

For ELISA analysis, 96 well plates were coated with P501S peptide 296-322 (referred to as P501-long), an irrelevant P775 peptide, P501S-N, P501TR2, P501S-long-KLH, P501S peptide 306-319 (referred to as P501-short)-KLH, or the irrelevant peptide 2073-KLH, all at a concentration of 2 ug/ml and allowed to incubate for 60 minutes at 37 °C. After coating, plates were washed 5X with PBS + 0.1% Tween and then blocked with PBS, 0.5% BSA, 0.4% Tween20 for 2 hours at room temperature. Following the addition of supernatants or purified mAb, the plates were incubated for 60 minutes at room temperature. Plates were washed as above and donkey anti-mouse IgHRP-linked secondary antibody was added and incubated for 30 minutes at room temperature, followed by a final washing as above. TMB peroxidase substrate was added and incubated 15 minutes at room temperature in the dark. The reaction was stopped by the addition of 1N H<sub>2</sub>SO<sub>4</sub> and the OD was read at 450 nM. All three hybrid clones secreted mAb that recognized peptide 296-322 and the recombinant protein P501N.

For FACS analysis, HEK293 cells were transiently transfected with a P501S/VR1012 expression constructs using Fugene 6 reagent. After 2 days of culture, cells were harvested and washed, then incubated with purified 4G5 mAb for 30 minutes on ice. After several washes in PBS, 0.5% BSA, 0.01% azide, goat anti-mouse Ig-FITC was added to the cells and incubated for 30 minutes on ice. Cells were washed and resuspended in wash buffer including 1% propidium iodide and subjected to FACS analysis. The FACS analysis confirmed that amino acids 296-322 of P501S are in an extracellular domain and are cell surface expressed.

The chromosomal location of P501S was determined using the GeneBridge 4 Radiation Hybrid panel (Research Genetics). The PCR primers of SEQ ID NO: 528 and 529 were employed in PCR with DNA pools from the hybrid panel according to the manufacturer's directions. After 38 cycles of amplification, the reaction products were separated on a 1.2% agarose gel, and the results were analyzed through the Whitehead Institute/MIT Center for Genome Research web server

(<http://www-genome.wi.mit.edu/cgi-bin/contig/rhmapper.pl>) to determine the probable chromosomal location. Using this approach, P501S was mapped to the long arm of chromosome 1 at WI-9641 between q32 and q42. This region of chromosome 1 has been linked to prostate cancer susceptibility in hereditary prostate cancer (Smith *et al.* *Science* 274:1371-1374, 1996 and Berthon *et al.* *Am. J. Hum. Genet.* 62:1416-1424, 1998). These results suggest that P501S may play a role in prostate cancer malignancy.

## EXAMPLE 20

### REGULATION OF EXPRESSION OF THE PROSTATE-SPECIFIC ANTIGEN P501S

10

Steroid (androgen) hormone modulation is a common treatment modality in prostate cancer. The expression of a number of prostate tissue-specific antigens have previously been demonstrated to respond to androgen. The responsiveness of the prostate-specific antigen P501S to androgen treatment was examined in a tissue culture system as follows.

15

Cells from the prostate tumor cell line LNCaP were plated at  $1.5 \times 10^6$  cells/T75 flask (for RNA isolation) or  $3 \times 10^5$  cells/well of a 6-well plate (for FACS analysis) and grown overnight in RPMI 1640 media containing 10% charcoal-stripped fetal calf serum (BRL Life Technologies, Gaithersburg, MD). Cell culture was continued for an additional 72 hours in RPMI 1640 media containing 10% charcoal-stripped fetal calf serum, with 1 nM of the synthetic androgen Methyltrienolone (R1881; New England Nuclear) added at various time points. Cells were then harvested for RNA isolation and FACS analysis at 0, 1, 2, 4, 8, 16, 24, 28 and 72-hours post androgen addition. FACS analysis was performed using the anti-P501S antibody 10E3-G4-D3 and permeabilized cells.

20

25

For Northern analysis, 5-10 micrograms of total RNA was run on a formaldehyde denaturing gel, transferred to Hybond-N nylon membrane (Amersham Pharmacia Biotech, Piscataway, NJ), cross-linked and stained with methylene blue. The filter was then prehybridized with Church's Buffer (250 mM  $\text{Na}_2\text{HPO}_4$ , 70 mM  $\text{H}_3\text{PO}_4$ , 1 mM EDTA, 1% SDS, 1% BSA in pH 7.2) at 65 °C for 1 hour. P501S DNA was

30

labeled with  $^{32}\text{P}$  using High Prime random-primed DNA labeling kit (Boehringer Mannheim). Unincorporated label was removed using MicroSpin S300-HR columns (Amersham Pharmacia Biotech). The RNA filter was then hybridized with fresh Church's Buffer containing labeled cDNA overnight, washed with 1X SCP (0.1 M NaCl, 0.03 M  $\text{Na}_2\text{HPO}_4 \cdot 7\text{H}_2\text{O}$ , 0.001 M  $\text{Na}_2\text{EDTA}$ ), 1% sarkosyl (n-lauroylsarcosine) and exposed to X-ray film.

Using both FACS and Northern analysis, P501S message and protein levels were found to increase in response to androgen treatment.

10

## EXAMPLE 20

## PREPARATION OF FUSION PROTEINS OF PROSTATE-SPECIFIC ANTIGENS

The example describes the preparation of a fusion protein of the prostate-specific antigen P703P and a truncated form of the known prostate antigen PSA. The truncated form of PSA has a 21 amino acid deletion around the active serine site. The expression construct for the fusion protein also has a restriction site at 3' end, immediately prior to the termination codon, to aid in adding cDNA for additional antigens.

The full-length cDNA for PSA was obtained by RT-PCR from a pool of RNA from human prostate tumor tissues using the primers of SEQ ID NO: 607 and 608, and cloned in the vector pCR-Blunt II-TOPO. The resulting cDNA was employed as a template to make two different fragments of PSA by PCR with two sets of primers (SEQ ID NO: 609 and 610; and SEQ ID NO: 611 and 612). The PCR products having the expected size were used as templates to make truncated forms of PSA by PCR with the primers of SEQ ID NO: 611 and 613, which generated PSA (delta 208-218 in amino acids). The cDNA for the mature form of P703P with a 6X histidine tag at the 5' end, was prepared by PCR with P703P and the primers of SEQ ID NO: 614 and 615. The cDNA for the fusion of P703P with the truncated form of PSA (referred to as FOPP) was then obtained by PCR using the modified P703P cDNA and the truncated form of PSA cDNA as templates and the primers of SEQ ID NO: 614 and 615. The FOPP



cDNA was cloned into the NdeI site and XhoI site of the expression vector pCRX1, and confirmed by DNA sequencing. The determined cDNA sequence for the fusion construct FOPP is provided in SEQ ID NO: 616, with the amino acid sequence being provided in SEQ ID NO: 617.

- 5                   The fusion FOPP was expressed as a single recombinant protein in *E. coli* as follows. The expression plasmid pCRX1FOPP was transformed into the *E. coli* strain BL21-CodonPlus RIL. The transformant was shown to express FOPP protein upon induction with 1 mM IPTG. The culture of the corresponding expression clone was inoculated into 25 ml LB broth containing 50 ug/ml kanamycin and 34 ug/ml
- 10 chloramphenicol, grown at 37 °C to OD600 of about 1, and stored at 4 °C overnight. The culture was diluted into 1 liter of TB LB containing 50 ug/ml kanamycin and 34 ug/ml chloramphenicol, and grown at 37 °C to OD600 of 0.4. IPTG was added to a final concentration of 1 mM, and the culture was incubated at 30 °C for 3 hours. The cells were pelleted by centrifugation at 5,000 RPM for 8 min. To purify the protein, the
- 15 cell pellet was suspended in 25 ml of 10 mM Tris-Cl pH 8.0, 2mM PMSF, complete protease inhibitor and 15 ug lysozyme. The cells were lysed at 4 °C for 30 minutes, sonicated several times and the lysate centrifuged for 30 minutes at 10,000 x g. The precipitate, which contained the inclusion body, was washed twice with 10 mM Tris-Cl pH 8.0 and 1% CHAPS. The inclusion body was dissolved in 40 ml of 10 mM Tris-Cl
- 20 pH 8.0, 100 mM sodium phosphate and 8 M urea. The solution was bound to 8 ml Ni-NTA (Qiagen) for one hour at room temperature. The mixture was poured into a 25 ml column and washed with 50 ml of 10 mM Tris-Cl pH 6.3, 100 mM sodium phosphate, 0.5% DOC and 8M urea. The bound protein was eluted with 350 mM imidazole, 10 mM Tris-Cl pH 8.0, 100 mM sodium phosphate and 8 M urea. The fractions containing
- 25 FOPP proteins were combined and dialyzed extensively against 10 mM Tris-Cl pH 4.6, aliquoted and stored at - 70 °C.

## EXAMPLE 21

REAL-TIME PCR CHARACTERIZATION OF THE PROSTATE-SPECIFIC ANTIGEN P501S IN  
PERIPHERAL BLOOD OF PROSTATE CANCER PATIENTS

5           Circulating epithelial cells were isolated from fresh blood of normal individuals and metastatic prostate cancer patients, mRNA isolated and cDNA prepared using real-time PCR procedures. Real-time PCR was performed with the Taqman<sup>TM</sup> procedure using both gene specific primers and probes to determine the levels of gene expression.

10           Epithelial cells were enriched from blood samples using an immunomagnetic bead separation method (Dynal A.S., Oslo, Norway). Isolated cells were lysed and the magnetic beads removed. The lysate was then processed for poly A+ mRNA isolation using magnetic beads coated with Oligo(dT)25. After washing the beads in buffer, bead/poly A+ RNA samples were suspended in 10 mM Tris HCl pH 8.0  
15           and subjected to reversed transcription. The resulting cDNA was subjected to real-time PCR using gene specific primers. Beta-actin content was also determined and used for normalization. Samples with P501S copies greater than the mean of the normal samples + 3 standard deviations were considered positive. Real time PCR on blood samples was performed using the Taqman<sup>TM</sup> procedure but extending to 50 cycles using  
20           forward and reverse primers and probes specific for P501S. Of the eight samples tested, 6 were positive for P501S and  $\beta$ -actin signal. The remaining 2 samples had no detectable  $\beta$ -actin or P501S. No P501S signal was observed in the four normal blood samples tested.

25

## EXAMPLE 22

EXPRESSION OF THE PROSTATE-SPECIFIC ANTIGENS P703P AND P501S IN  
SCID MOUSE-PASSAGED PROSTATE TUMORS

          When considering the effectiveness of antigens in the treatment of  
30       prostate cancer, the continued presence of the antigens in tumors during androgen

ablation therapy is important. The presence of the prostate-specific antigens P703P and P501S in prostate tumor samples grown in SCID mice in the presence of testosterone was evaluated as follows.

Two prostate tumors that had metastasized to the bone were removed  
5 from patients, implanted into SCID mice and grown in the presence of testosterone. Tumors were evaluated for mRNA expression of P703P, P501S and PSA using quantitative real time PCR with the SYBR green assay method. Expression of P703P and P501S in a prostate tumor was used as a positive control and the absence in normal intestine and normal heart as negative controls. In both cases, the specific mRNA was  
10 present in late passage tumors. Since the bone metastases were grown in the presence of testosterone, this implies that the presence of these genes would not be lost during androgen ablation therapy.

#### EXAMPLE 23

##### 15 ANTI-P503S MONOCLONAL ANTIBODY INHIBITS TUMOR GROWTH *IN VIVO*

The ability of the anti-P503S monoclonal antibody 20D4 to suppress tumor formation in mice was examined as follows.

Ten SCID mice were injected subcutaneously with HEK293 cells that expressed P503S. Five mice received 150 micrograms of 20D4 intravenously at day 0  
20 (time of tumor cell injection), day 5 and day 9. Tumor size was measured for 50 days. Of the five animals that received no 20D4, three formed detectable tumors after about 2 weeks which continued to enlarge throughout the study. In contrast, none of the five mice that received 20D4 formed tumors. These results demonstrate that the anti-P503S Mab 20D4 displays potent anti-tumor activity *in vivo*.

25

#### EXAMPLE 24

##### CHARACTERIZATION OF A T CELL RECEPTOR CLONE FROM A P501S-SPECIFIC T CELL CLONE

30 T cells have a limited lifespan. However, cloning of T cell receptor (TCR) chains and subsequent transfer essentially enables infinite propagation of the T

cell specificity. Cloning of tumor-antigen TCR chains allows the transfer of the specificity into T cells isolated from patients that share the TCR MHC-restricting allele. Such T cells could then be expanded and used in adoptive transfer settings to introduce the tumor antigen specificity into patients carrying tumors that express the antigen. T cell receptor alpha and beta chains from a CD8 T cell clone specific for the prostate-specific antigen P501S were isolated and sequenced as follows.

Total mRNA from  $2 \times 10^6$  cells from CTL clone 4E5 (described above in Example 12) was isolated using Trizol reagent and cDNA was synthesized. To determine Va and Vb sequences in this clone, a panel of Va and Vb subtype-specific primers was synthesized and used in RT-PCR reactions with cDNA generated from each of the clones. The RT-PCR reactions demonstrated that each of the clones expressed a common Vb sequence that corresponded to the Vb7 subfamily. Furthermore, using cDNA generated from the clone, the Va sequence expressed was determined to be Va6. To clone the full TCR alpha and beta chains from clone 4E5, primers were designed that spanned the initiator and terminator-coding TCR nucleotides. The primers were as follows: TCR Valpha-6 5'(sense): GGATCC---GCCGCCACC---ATGTCACCTTTCTAGCCTGCT (SEQ ID NO: 756) BamHI site Kozak TCR alpha sequence TCR alpha 3' (antisense): GTCGAC---TCAGCTGGACCACAGCCGCAG (SEQ ID NO: 757) Sall site TCR alpha constant sequence TCR Vbeta-7. 5'(sense): GGATCC---GCCGCCACC---ATGGGCTGCAGGCTGCTCT (SEQ ID NO: 758) BamHI site Kozak TCR alpha sequence TCR beta 3' (antisense): GTCGAC---TCAGAAATCCTTTCTCTTGAC (SEQ ID NO: 759) Sall site TCR beta constant sequence. Standard 35 cycle RT-PCR reactions were established using cDNA synthesized from the CTL clone and the above primers, employing the proofreading thermostable polymerase PWO (Roche, Nutley, NJ).

The resultant specific bands (approx. 850 bp for alpha and approx. 950 for beta) were ligated into the PCR blunt vector (Invitrogen) and transformed into *E. coli*. *E. coli* transformed with plasmids containing full-length alpha and beta chains were identified, and large scale preparations of the corresponding plasmids were generated. Plasmids containing full-length TCR alpha and beta chains were submitted

for sequencing. The sequencing reactions demonstrated the cloning of full-length TCR alpha and beta chains with the determined cDNA sequences for the Vb and Va chains being shown in SEQ ID NO: 760 and 761, respectively. The corresponding amino acid sequences are shown in SEQ ID NO: 762 and 763, respectively. The Va sequence was  
5 shown by nucleotide sequence alignment to be 99% identical (347/348) to Va6.2, and the Vb to be 99% identical to Vb7 (336/338).

From the foregoing it will be appreciated that, although specific embodiments of the invention have been described herein for purposes of illustration,  
10 various modifications may be made without deviating from the spirit and scope of the invention. Accordingly, the invention is not limited except as by the appended claims.

## CLAIMS

What is Claimed:

1. An isolated polynucleotide comprising a sequence selected from the group consisting of:

(a) sequences provided in SEQ ID NO: 1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 and 384-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-626, 630, 631, 634, 636, 639-655, 674, 680, 681, 711, 713, 716, 720-722, 735, 737-739, 751, 753, 764, 765, 773-776 and 786-788;

(b) complements of the sequences provided in SEQ ID NO: 1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 and 384-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-626, 630, 631, 634, 636, 639-655, 674, 680, 681, 711, 713, 716, 720-722, 735, 737-739, 751, 753, 764, 765, 773-776 and 786-788;

(c) sequences consisting of at least 20 contiguous residues of a sequence provided in SEQ ID NO: 1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 and 384-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-626, 630, 631, 634, 636, 639-655, 674, 680, 681, 711, 713, 716, 720-722, 735, 737-739, 751, 753, 764, 765, 773-776 and 786-788;

(d) sequences that hybridize to a sequence provided in SEQ ID NO: 1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 and 384-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-626, 630, 631, 634, 636, 639-655, 674, 680, 681, 711, 713, 716, 720-722, 735, 737-739, 751, 753, 764, 765, 773-776 and 786-788 under moderately stringent conditions;

(e) sequences having at least 75% identity to a sequence of SEQ ID NO: 1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-

375, 381, 382 and 384-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-626, 630, 631, 634, 636, 639-655, 674, 680, 681, 711, 713, 716, 720-722, 735, 737-739, 751, 753, 764, 765, 773-776 and 786-788;

(f) sequences having at least 90% identity to a sequence of SEQ ID NO: 1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 and 384-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-626, 630, 631, 634, 636, 639-655, 674, 680, 681, 711, 713, 716, 720-722, 735, 737-739, 751, 753, 764, 765, 773-776 and 786-788; and

(g) degenerate variants of a sequence provided in SEQ ID NO: 1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 and 384-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-626, 630, 631, 634, 636, 639-655, 674, 680, 681, 711, 713, 716, 720-722, 735, 737-739, 751, 753, 764, 765, 773-776 and 786-788.

2. An isolated polypeptide comprising an amino acid sequence selected from the group consisting of:

(a) sequences recited in SEQ ID NO: 112-114, 172, 176, 178, 327, 329, 331, 336, 339, 376-380, 383, 477-483, 496, 504, 505, 519, 520, 522, 525, 527, 532, 534, 537-551, 553-568, 573-586, 588-590, 592, 627-629, 632, 633, 635, 637, 638, 656-671, 675, 683, 684, 710, 712, 714, 715, 717-719, 723-734, 736, 740-750, 752, 754, 755, 766-772, 777-785 and 789-791;

(b) sequences having at least 70% identity to a sequence of SEQ ID NO: 112-114, 172, 176, 178, 327, 329, 331, 336, 339, 376-380, 383, 477-483, 496, 504, 505, 519, 520, 522, 525, 527, 532, 534, 537-551, 553-568, 573-586, 588-590, 592, 627-629, 632, 633, 635, 637, 638, 656-671, 675, 683, 684, 710, 712, 714, 715, 717-719, 723-734, 736, 740-750, 752, 754, 755, 766-772, 777-785 and 789-791;

(c) sequences having at least 90% identity to a sequence of SEQ ID NO: 112-114, 172, 176, 178, 327, 329, 331, 336, 339, 376-380, 383, 477-483, 496, 504, 505, 519, 520, 522, 525, 527, 532, 534, 537-551, 553-568, 573-586, 588-590, 592, 627-

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- (d) sequences encoded by a polynucleotide of claim 1;
- (e) sequences having at least 70% identity to a sequence encoded by a polynucleotide of claim 1; and
- (f) sequences having at least 90% identity to a sequence encoded by a polynucleotide of claim 1.

3. An expression vector comprising a polynucleotide of claim 1 operably linked to an expression control sequence.

4. A host cell transformed or transfected with an expression vector according to claim 3.

5. An isolated antibody, or antigen-binding fragment thereof, that specifically binds to a polypeptide of claim 2.

6. A method for detecting the presence of a cancer in a patient, comprising the steps of:

- (a) obtaining a biological sample from the patient;
- (b) contacting the biological sample with a binding agent that binds to a polypeptide of claim 2;
- (c) detecting in the sample an amount of polypeptide that binds to the binding agent; and
- (d) comparing the amount of polypeptide to a predetermined cut-off value and therefrom determining the presence of a cancer in the patient.

7. A fusion protein comprising at least one polypeptide according to claim 2.



8. The fusion protein of claim 7, wherein the fusion protein comprises a sequence selected from the group consisting of:

(a) sequences provided in SEQ ID NO: 682, 692, 695, 699, 703 and 709; and

(b) sequences encoded by SEQ ID NO: 679, 691, 696, 700, 704 and 708.

9. An oligonucleotide that hybridizes to a sequence recited in SEQ ID NO: 1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 and 384-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-626, 630, 631, 634, 636, 639-655, 674, 680, 681, 711, 713, 716, 720-722, 735, 737-739, 751, 753, 764, 765, 773-776 or 786-788 under moderately stringent conditions.

10. A method for stimulating and/or expanding T cells specific for a tumor protein, comprising contacting T cells with at least one component selected from the group consisting of:

(a) polypeptides according to claim 2;  
(b) polynucleotides according to claim 1; and  
(c) antigen-presenting cells that express a polypeptide according to claim 1,

under conditions and for a time sufficient to permit the stimulation and/or expansion of T cells.

11. An isolated T cell population, comprising T cells prepared according to the method of claim 10.

12. A composition comprising a first component selected from the group consisting of physiologically acceptable carriers and immunostimulants, and a **second component selected from the group consisting of:**

- (a) polypeptides according to claim 2;
- (b) polynucleotides according to claim 1;
- (c) antibodies according to claim 5;
- (d) fusion proteins according to claim 7;
- (e) T cell populations according to claim 11; and
- (f) antigen presenting cells that express a polypeptide according to claim 2.

13. A method for stimulating an immune response in a patient, comprising administering to the patient a composition of claim 12.

14. A method for the treatment of a cancer in a patient, comprising administering to the patient a composition of claim 12.

15. A method for determining the presence of a cancer in a patient, comprising the steps of:

- (a) obtaining a biological sample from the patient;
- (b) contacting the biological sample with an oligonucleotide according to claim 9;
- (c) detecting in the sample an amount of a polynucleotide that hybridizes to the oligonucleotide; and
- (d) compare the amount of polynucleotide that hybridizes to the oligonucleotide to a predetermined cut-off value, and therefrom determining the presence of the cancer in the patient.

16. A diagnostic kit comprising at least one oligonucleotide according to claim 9.

17. A diagnostic kit comprising at least one antibody according to claim 5 and a detection reagent, wherein the detection reagent comprises a reporter group.

18. A method for inhibiting the development of a cancer in a patient, comprising the steps of:

(a) incubating CD4<sup>+</sup> and/or CD8<sup>+</sup> T cells isolated from a patient with at least one component selected from the group consisting of: (i) polypeptides according to claim 2; (ii) polynucleotides according to claim 1; and (iii) antigen presenting cells that express a polypeptide of claim 2, such that T cell proliferate; and

(b) administering to the patient an effective amount of the proliferated T cells,

thereby inhibiting the development of a cancer in the patient.

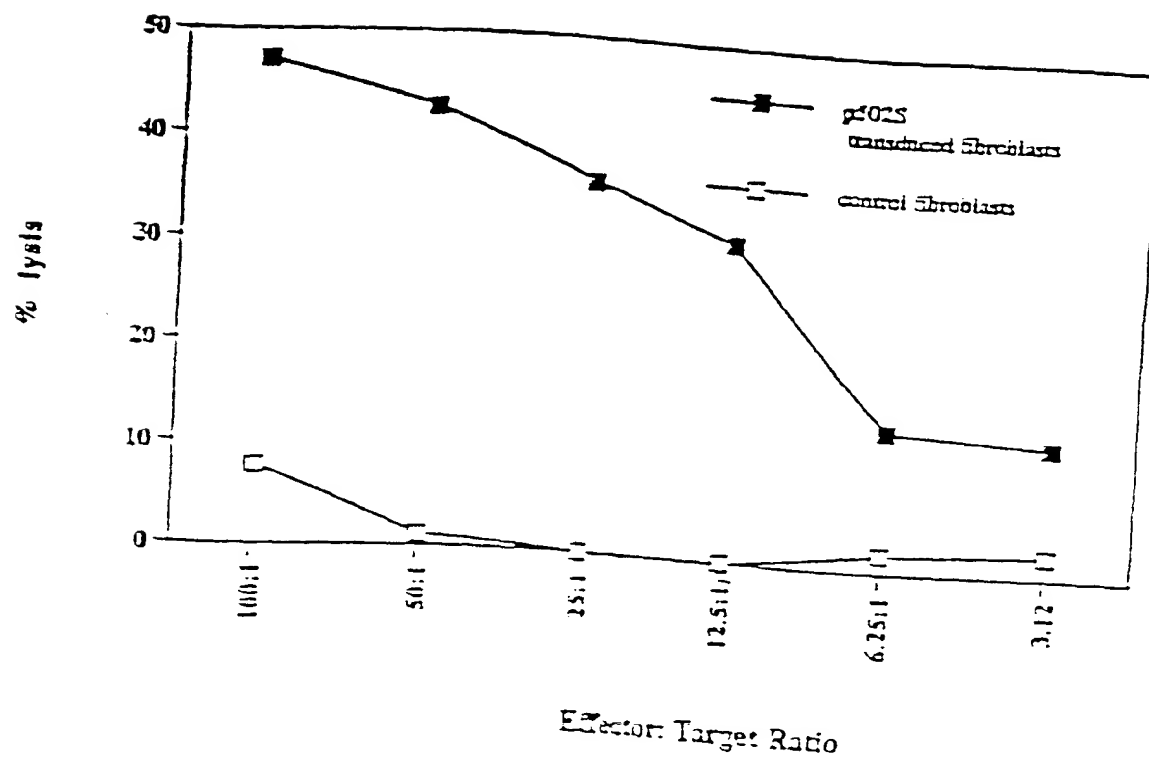


Fig. 1

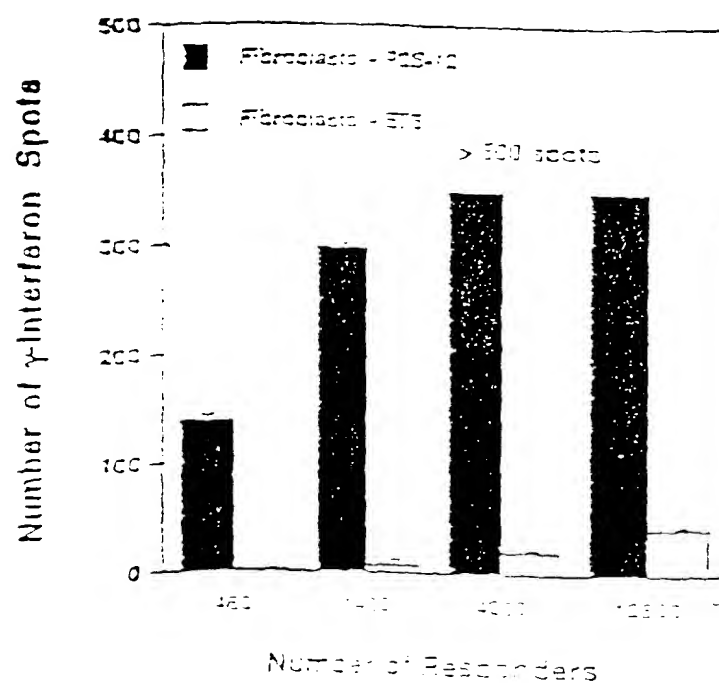


Fig. 2A

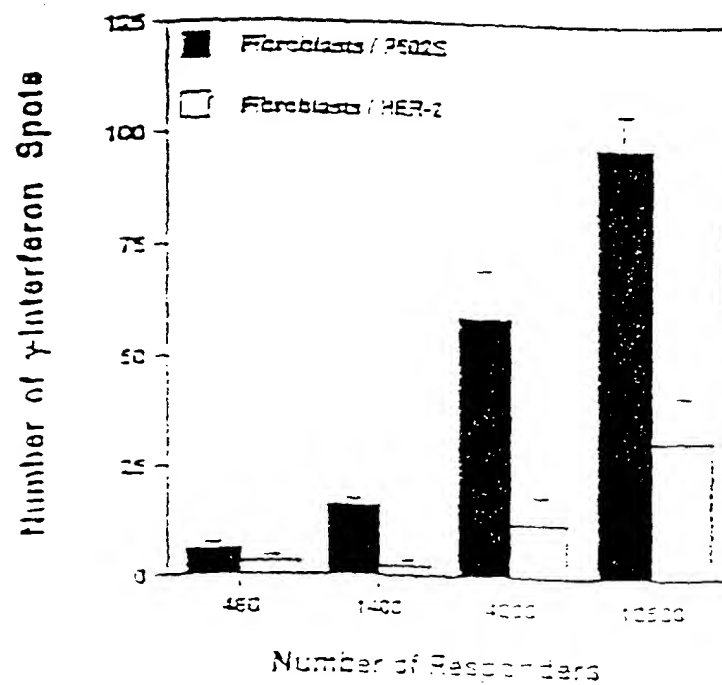


Fig. 25

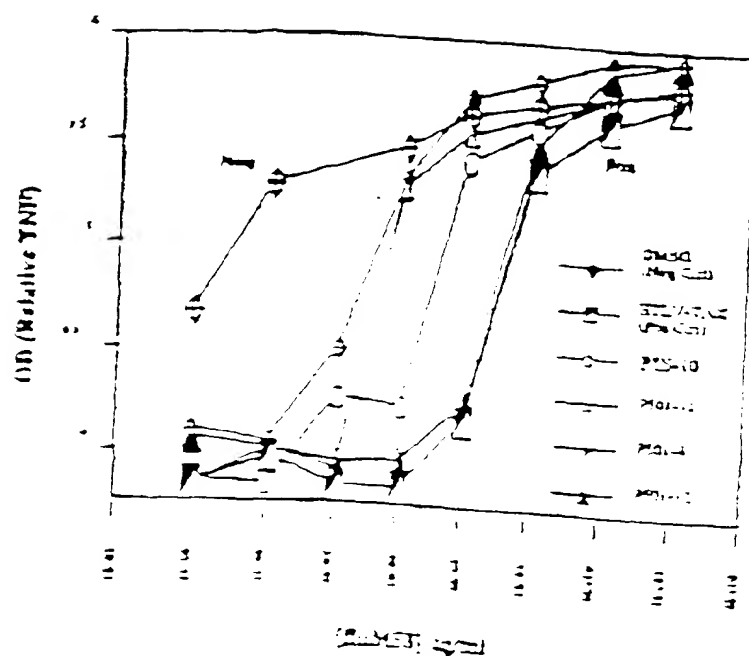


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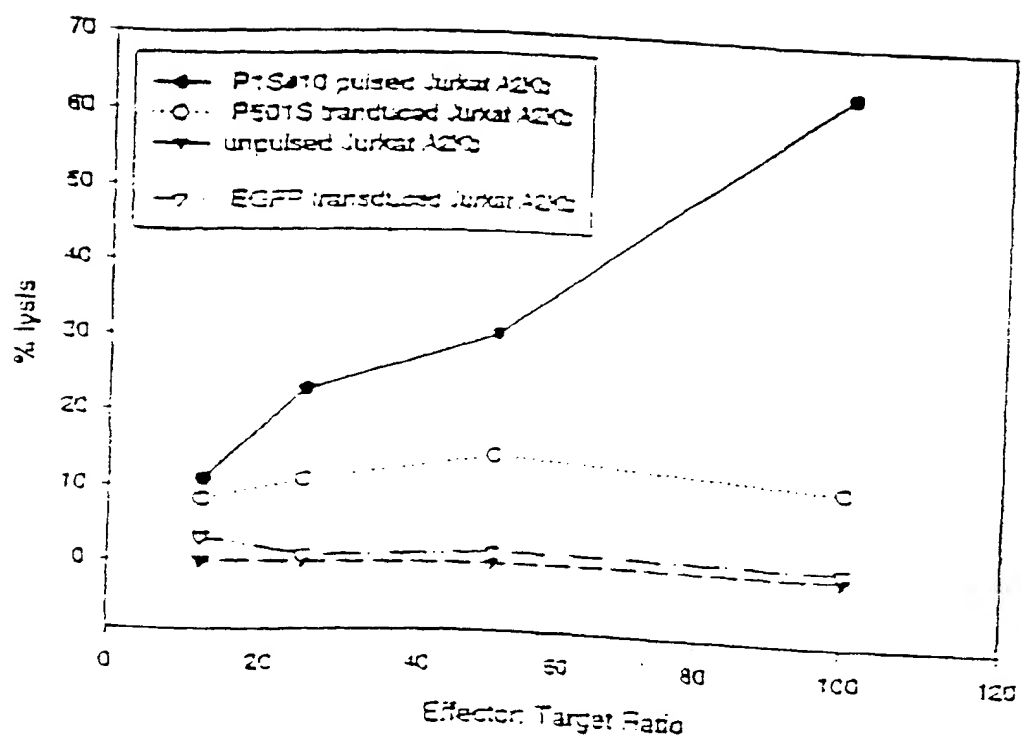


Fig. 4



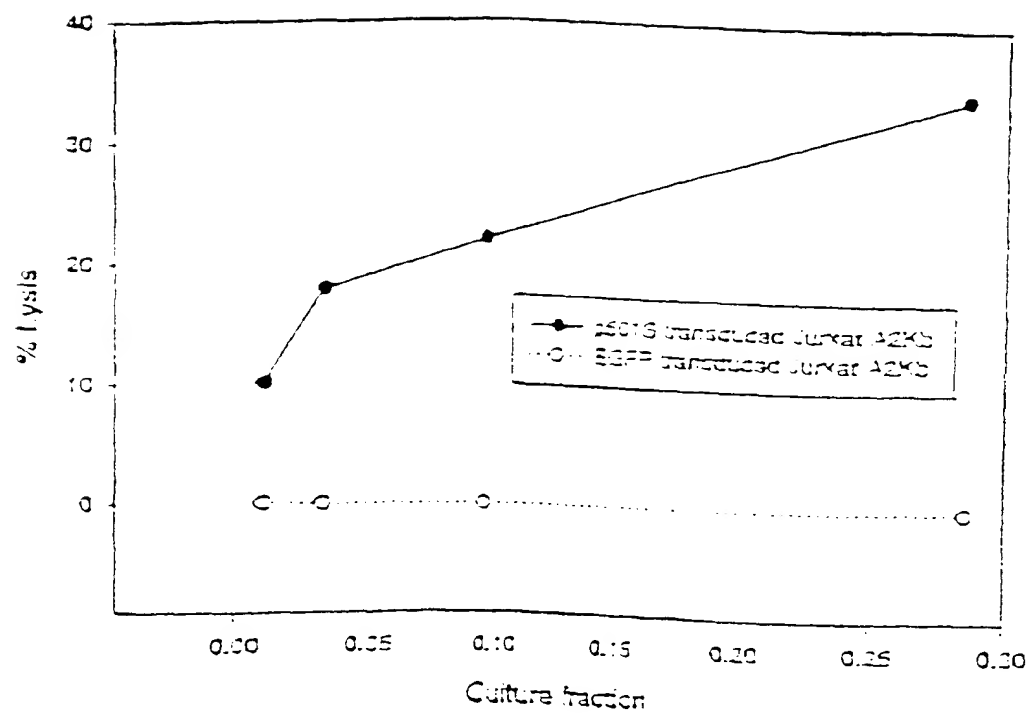


Fig. 5

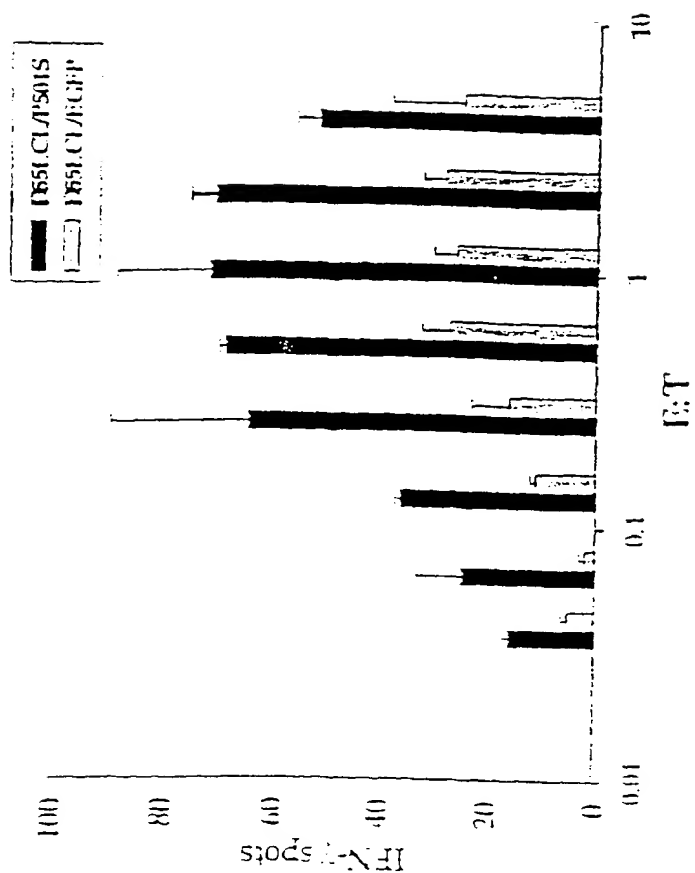


Fig. 6B

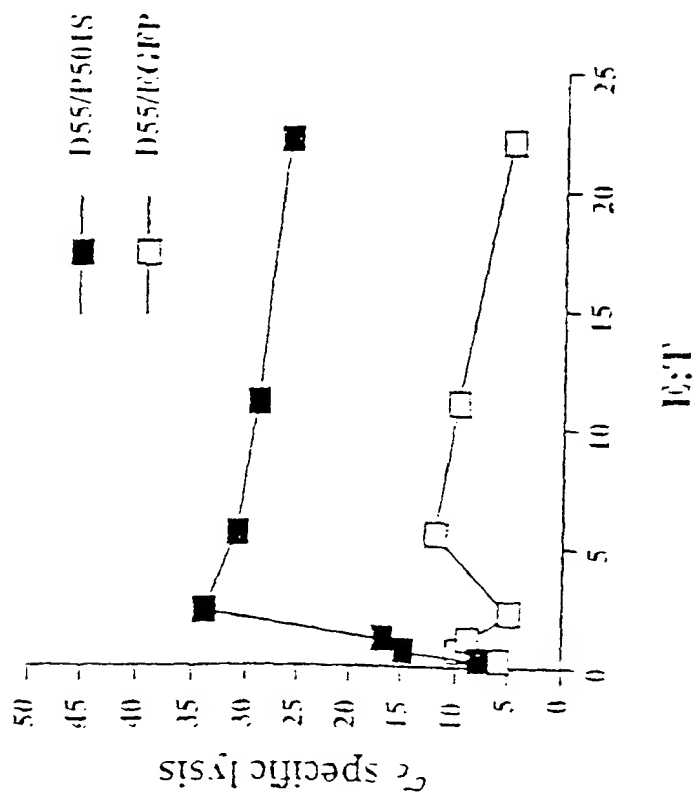
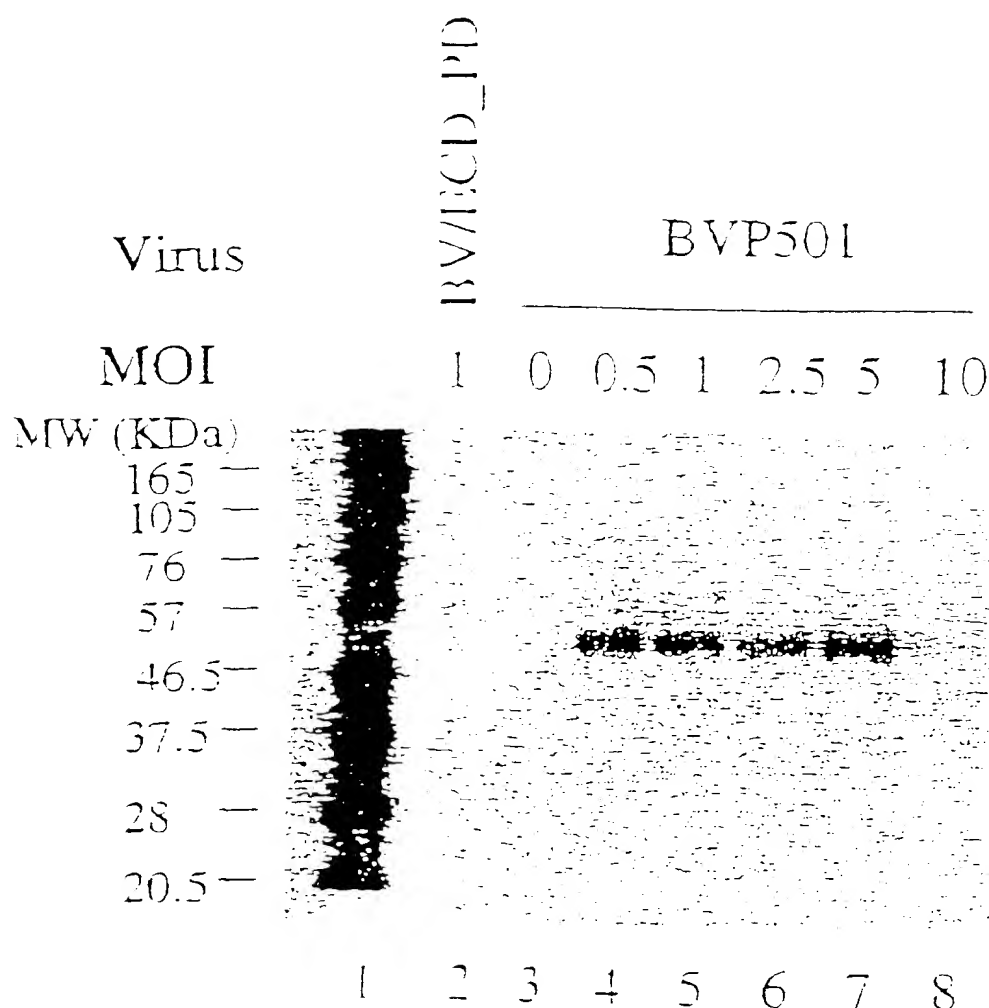


Fig. 6A

# Expression of P501S by the Baculovirus Expression System



0.6 million high 5 cells in 6-well plate were infected with an unrelated control virus BV/ECD\_PD (lane 2) without virus (lane 3), or with recombinant baculovirus for P501S at different MOIs (lane 4-8). Cell lysates were run on SDS-PAGE under the reducing conditions and analyzed by Western blot with a monoclonal antibody against P501S (10E8-G4D3). Lane 1 is the biotinylated protein molecular weight marker (500 kDa).

Fig. 7



# Figure 1. Schematic of P501S with predicted transmembrane, cytoplasmic, and extracellular regions

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Underlined sequence: Predicted transmembrane domain; Bold sequence: Predicted extracellular domain;  
 Italic sequence: Predicted intracellular domain. Sequence in bold/underlined: used to generate polyclonal rabbit serum

Localization of domains predicted using HMMTOP (G.E. Tusnady and I. Simon (1998) Principles  
 Governing Amino Acid Composition of Integral Membrane Proteins: Applications to topology Prediction. J Mol Biol. 283,  
 489-506.

## Genomic Map of (5) Corixa Candidate Genes

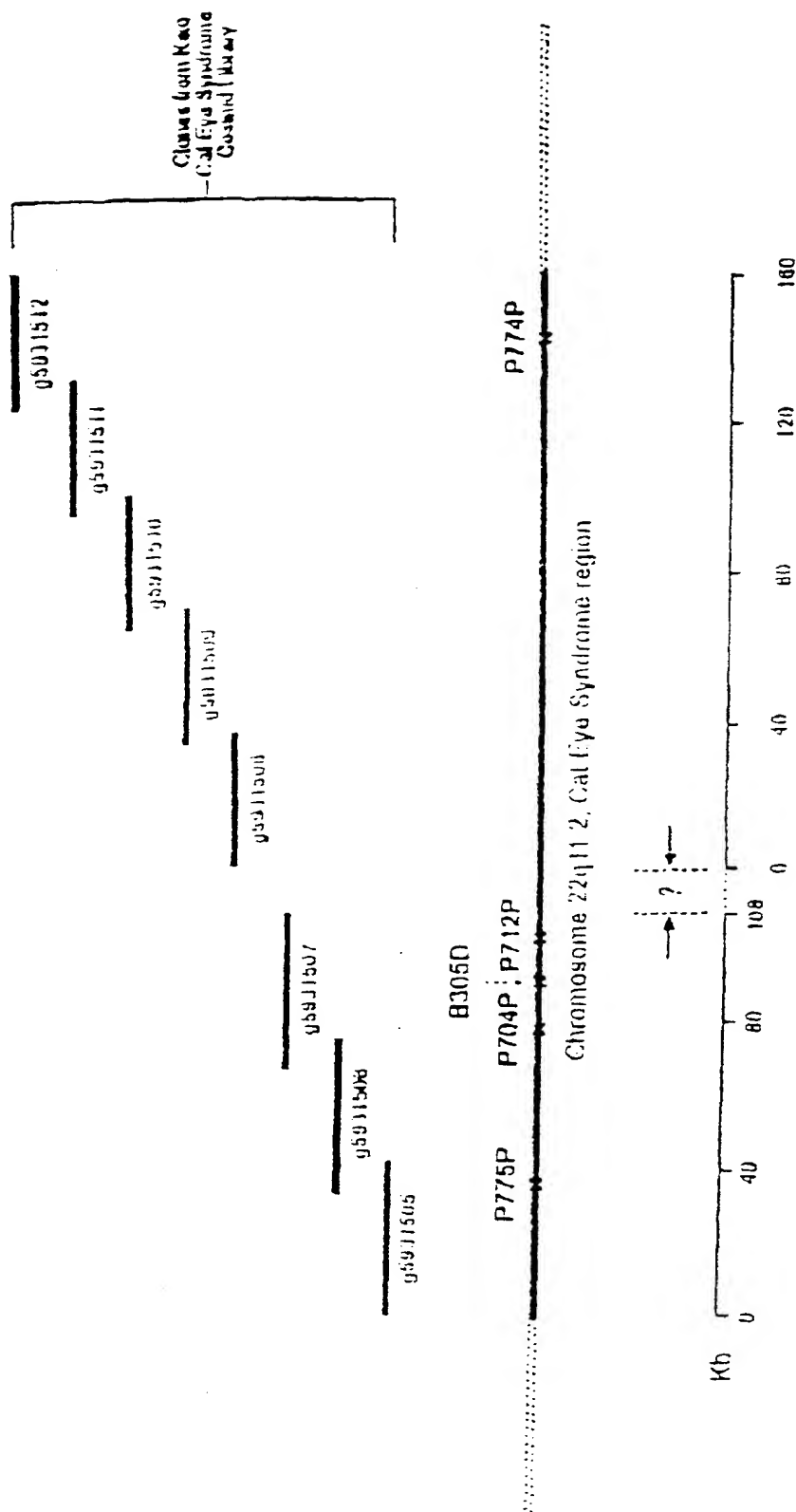


Fig. 10

**FIGURE 4. Elisa assay of rabbit polyclonal antibody specificity**

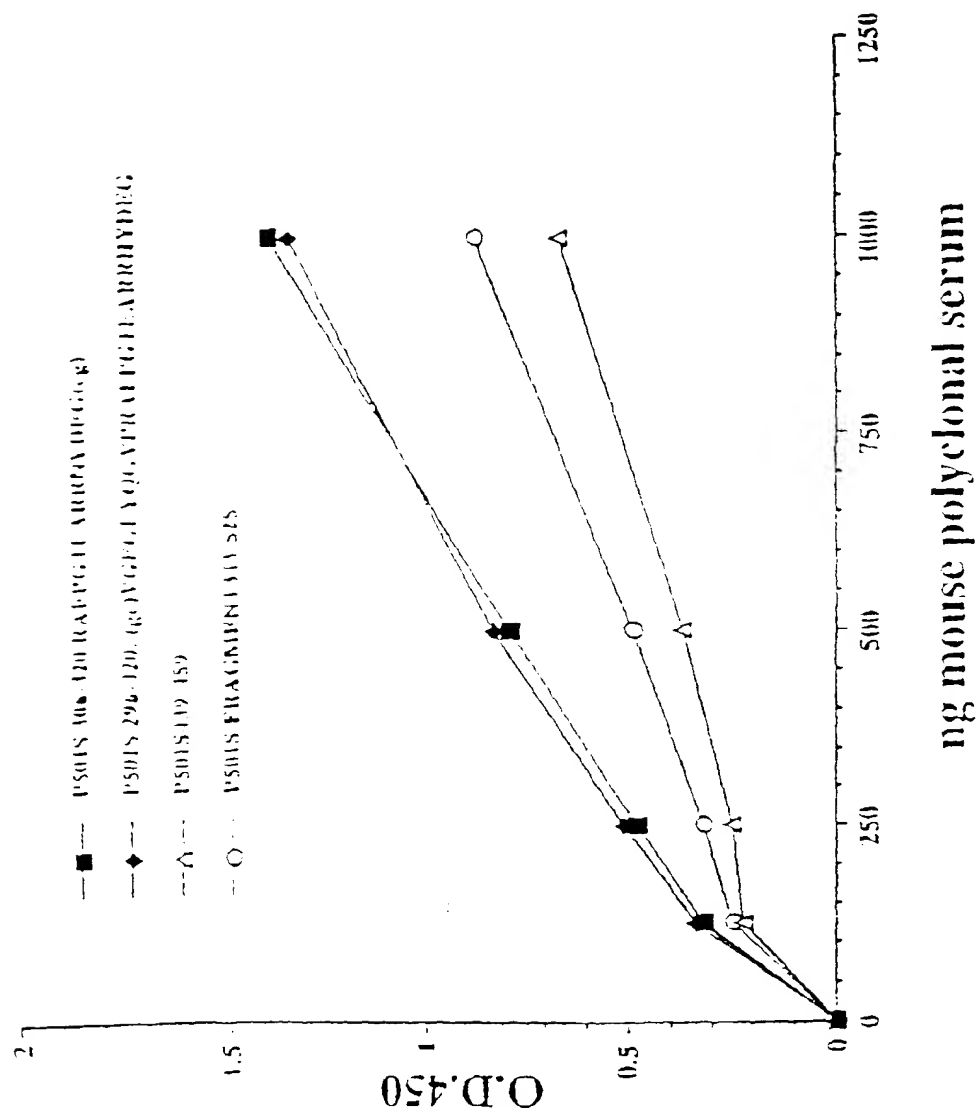


Fig. 11

## SEQUENCE LISTING

<110> Corixa Corporation  
 Smithkline Beechan Biologicals S.A.  
 Xu, Jiangchun  
 Dillon, Davin C.  
 Mitcham, Jennifer L.  
 Harlocker, Susan L.  
 Jiang, Yuqui  
 Reed, Steven G.  
 Kalos, Michael D.  
 Fanger, Gary R.  
 Retter, Marc W.  
 Stolk, John A.  
 Day, Craig H.  
 Skeiky, Yasir A.W.  
 Wang, Aijun  
 Meagher, Medeleine Joy  
 Vanderbrugge, Didier  
 Dewerchin, Marianne  
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gaatnttngg gaaaagggct tacaggacta gaaaccaaata angaaaanta atnntaangg      660
cnttatcntn aaaggtmata accnctccta tnatcccacc caatngnatt cccacnncn      720
acnattggat nccccanttc canaaanggc cccccccggt tgnannccnc cttttgttcc      780
cttnantgan ggttattcnc cctngcntt atcance      817

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```

<210> 8
<211> 799
<212> DNA
<213> Homo sapien

```

```

<220>
<221> misc_feature
<222> (1)...(799)
<223> n = A,T,C or G

```

```

<400> 8
catttcgggg tttactttct aaggaaagcc gagcggaagc tgctaacgtg ggaatcggtg      60
catgaaggaga actttctgct ggcaacgcgt agggacaagc gggagagcga ctccgagcgt      120
ctgaagcgca cgtcccagaa ggtggacttg gcaactgaaac agctgggaca catccgcgag      180
tacgaacagc gcctgaaagt gctggagcgg gaggtccagc agtgtagccg cgtcctgggg      240

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tgggtggccg	angcctganc	cgetctgcct	tgetgcccc	angtgggccc	ccaccccctg	300
acctgacctg	gtccaaacac	tgagccctgc	tggeggactt	caagganaac	ccccacangg	360
ggattttgct	cctanantaa	ggctcatctg	ggcctcggcc	ccccacactg	gttggccttg	420
tctttgangt	gagccccatg	tccatctggg	ccactgtcng	gaccaccttt	ngggagtgtt	480
ctccttacia	ccacannatg	cccggctcct	cccggaacc	<b>antccancc</b>	<b>tgngaaggat</b>	<b>540</b>
caagnccctg	atccactnnt	nctanaaccg	gcncncnccg	cngtgggaacc	cnccttntgt	600
tctttttent	tnagggttaa	tnnccgcttg	gccttnccan	ngtccctncc	nttttccnnt	660
gttnaaattg	ttangcnccc	nccnntcccn	cnnccnnan	cccgaaccnn	annttnnann	720
nccctggggg	nccnncngat	tgaccenncc	nccctntant	tgcnttnggg	nncnntgccc	780
ctttccctct	ngggannccg					799

&lt;210&gt; 9

&lt;211&gt; 801

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; (1)...(801)

&lt;223&gt; n = A,T,C or G

&lt;400&gt; 9

acgccttgat	cctcccaggc	tggtgactggt	tctgggagga	gccggggcatg	ctgtgggtttg	60
taangatgac	actcccaaag	gtggtcctga	cagtggccca	gatggacatg	gggctcacct	120
caaggacaag	gccaccagg	gccccggccg	aagccacat	gatccttact	ctatgagcaa	180
aatccctgt	gggggcttct	ccttgaagtc	cgccancagg	gctcagtctt	tggacccang	240
caggtcatgg	ggttgtngnc	caactggggg	ccncaacgca	aaanggcnc	gggcctcngn	300
cacccatccc	angacgcggc	tacactnctg	gacctccnc	tccaccactt	tcatgcgctg	360
ttentacccg	cgatntgttc	ccanctgttt	cngtgccnac	tccancttct	nggacgtgcg	420
ctacatacgc	ccggantcnc	nctcccgttt	tgctccctatc	cacgtncan	caacaaattt	480
cncctantg	caccnattcc	cacnttttnc	agntttccnc	nncgncttc	cttntaaaag	540
ggttganc	cggaataatc	cccaaagggg	gggggcccng	tacccaactn	ccccctnata	600
gctgaantcc	ccatnaccnn	gnctcnatgg	anccntccnt	tttaannacn	ttctnaactt	660
gggaananc	ctcgnccntn	ccccnttaa	tccncccttg	cnangnnent	ccccnntcc	720
nccnntng	gcntntnann	cnaaaaaggc	cnnnancaa	tctcctnnen	cctcanttcg	780
ccanccctcg	aaatcgccn	c				801

&lt;210&gt; 10

&lt;211&gt; 789

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; (1)...(789)

&lt;223&gt; n = A,T,C or G

&lt;400&gt; 10

cagtctatnt	ggccagtgtg	gcagctttcc	ctgtggetgc	cggtgccaca	tgccctgtccc	60
acagtgtggc	cgtggtgaca	gcttcagccg	ccctcaccgg	gttcaccttc	tcagccctgc	120
agatccctgc	ctacacactg	gcctccctct	accaccggga	gaagcagggt	ttcctgcccc	180
aataccgagg	ggacactgga	ggtgctagca	gtgaggacag	cctgatgacc	agcttcctgc	240
caggccctaa	gcctggagct	cccttcccta	atggacacgt	gggtgctgga	ggcagtggcc	300
tgctccacc	tccaccggcg	ctctgcccgg	cctctgcctg	tgatgtctcc	gtacgtgtgg	360
tggtgggtga	gccaccgan	gccagggtgg	ttccggggccg	gggcactctgc	ctggacctcg	420
ccatccctga	tagtgcttcc	tgetgtccca	ngtggcccca	tcctgttcta	tgggctccat	480
tgtccagctc	agccagtctg	tactgccta	tatgggtgtc	gccgcaggcc	tgggtctggt	540
cccatttact	ttgtacaca	ggtantattt	gacaagaacg	anttggccaa	atactcagcg	600

ttaaaaaatt	ccagcaacat	tgggggtgga	aggcctgcct	cactgggtcc	aactccccgc	660
tccgtgtaac	cccatggggc	tgccggcttg	gccgccaat	tctgttgctg	ccaaantnat	720
atgacctctc	gttgccacct	gttgctggct	gaagtgcnta	cngcncanct	nggggggtng	780
gggtgtccc						789

<210> 11  
 <211> 772  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(772)  
 <223> n = A,T,C or G

<400> 11						
cccaccctac	ccaaatatta	gacaccaaca	cagaaaagct	agcaatggat	tcccttctac	60
tttgttaaat	aaataagtta	aatatTTaaa	tgccgtgtgc	tctgtgatgg	caacagaagg	120
accaacaggc	cacatccctga	taaaaggtaa	gaggggggtg	gatcagcaaa	aagacagtgc	180
tgtgggctga	ggggacctgg	ttcttgtgtg	ttgcccctca	ggactcttcc	cctacaaata	240
actttcatat	gttcaaattcc	catggaggag	tgtttcatcc	tagaaactcc	catgcaagag	300
ctacattaaa	cgaagctgca	ggttaagggg	cttanagatg	ggaaaccagg	tgactgagtt	360
tattcagctc	ccaaaaaccc	ttctctaggt	gtgtctcaac	taggaggcta	gctgttaacc	420
ctgagcctgg	gtaateccacc	tgcaagatcc	ccgcattcca	gtgcatggaa	cccttctggc	480
ctccctgtat	aagtccagac	tgaaaccccc	ttggaaggnc	tccagtcagg	cagccctana	540
aactggggaa	aaaagaaaaa	gacgccccan	cccccagctg	tgcanctacg	cacctcaaca	600
gcacaggggtg	gcagcaaaaa	aaccacttta	ctttggcaca	aacaaaaaact	nggggggggca	660
accccggcac	cccnangggg	gttaacagga	ancngggnaa	cntggaaccc	aattnaggca	720
ggcccnccac	ccnaatntt	gctgggaaat	ttttcctccc	ctaaattntt	tc	772

<210> 12  
 <211> 751  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(751)  
 <223> n = A,T,C or G

<400> 12						
gccccaatte	cagctgccac	accacccacg	gtgactgcat	tagttcggat	gtcatacaaa	60
agctgattga	agcaaccctc	tacttttttg	togtgagcct	tttgcttggg	gcaggtttca	120
ttggctgtgt	tggtgacgtt	gtcattgcaa	cagaatgggg	gaaaggcact	gttctctttg	180
aagtanggtg	agtcctcaaa	atccgtatag	ttgggtgaagc	cacagcactt	gagccctttc	240
atggtgggtg	tccacacttg	agtgaagtct	tccctgggaac	cataatcttt	cttgatggca	300
ggcactacca	gcaacgtcag	ggaagtgtct	agccattgtg	gtgtacacca	aggcgaccac	360
agcagctgcn	acctcagcaa	tgaagatgan	gaggangatg	aagaagaacg	tcncgagggc	420
acacttgctc	tcagtcttan	caccatanca	gcccntgaaa	accaananca	aagaccacna	480
cncgggtctc	gatgaagaaa	tnaccccnng	ttgacaaact	tgcatggcac	tggganccac	540
agtggcccna	aaaatcttca	aaaaggatgc	cccatcnatt	gaccccccaa	atgccactgt	600
ccaacagggg	ctgccccacn	cncnnaacga	tgancnatt	gnacaagatc	tncntggtct	660
tnatnaacnt	gaacctgcn	tngtggctcc	tgttcaggnc	cnnngcctga	cttctnaann	720
anngaacten	gaagncccca	cngganannc	g			751

<210> 13  
 <211> 729  
 <212> DNA

<213> Homo sapien

<220>

<221> misc\_feature

<222> (1)...(729)

<223> n = A,T,C or G

<400> 13

gagccaggcg	tccctctgcc	tgcccaactca	gtggcaacac	ccgggagctg	ttttgtcctt	60
tgtggancct	cagcagtncc	ctctttcaga	actcantgcc	aagancctg	aacaggagcc	120
accatgcagt	gcttcagctt	cattaagacc	atgatgatcc	tcttcaattt	gtcatctttt	180
ctgtgtggtg	cagccctggt	ggcagtgggc	atctgggtgt	caatcgatgg	ggcatccttt	240
ctgaagatct	tggggccact	gtcgtccagt	gccatgcagt	ttgtcaacgt	gggctaactc	300
ctcatcgag	ccggcggtgt	ggtcttagct	ctaggtttcc	tgggctgcta	tgggtgctaag	360
actgagagca	agtgtgccct	cgtgacgttc	ttcttcaccc	tcctcctcat	cttcattgct	420
gaggttgcaa	tgtgtgggtc	gccttgggtg	acaccacaat	ggctgagcac	ttcctgacgt	480
tgtgtgtaat	gcctgccatc	aanaaaagat	tatgggttcc	caggaanact	tactcaagt	540
gttggaaacac	caccatgaaa	gggctcaagt	gctgtggctt	cnnccaacta	tacggatttt	600
gaagantcac	ctacttcaaa	gaaaanagtg	cctttccccc	atttctgttg	caattgacaa	660
acgtccccaa	cacagccaat	tgaaaacctg	cacccaaccc	aaanggggtc	ccaaccnaaa	720
attnaaggg						729

<210> 14

<211> 816

<212> DNA

<213> Homo sapien

<220>

<221> misc\_feature

<222> (1)...(816)

<223> n = A,T,C or G

<400> 14

tgtctcttct	caaagttggt	cttgttgcca	taacaaccac	cataggtaaa	gcgggcgag	60
tgttcgtga	aggggttgta	gtaccagcgc	gggatgctct	ccttgacagag	tcctgtgtct	120
ggcaggtcca	cgcagtgcc	tttgtcactg	gggaaatgga	tgcgtggag	ctcgtcaaag	180
ccactcgtgt	atttttcaca	ggcagcctcg	tccgacgcgt	cggggcagtt	gggggtgtct	240
tcacactcca	ggaaactgtc	natgcagcag	ccattgctgc	agcggaactg	ggtgggctga	300
cangtgccag	agcacactgg	atggcgctt	tccatggnan	gggccctgng	ggaaagtccc	360
tganccccc	anctgcctct	caaangcccc	accttgacac	ccccgacagg	ctagaatgga	420
atcttcttcc	cgaaaggtag	ttnttcttgt	tgcccaancc	anccccntaa	acaaactctt	480
gcanatctgc	tccgnggggg	tentantacc	ancgtgggaa	agaaccccca	ggcngcgaac	540
caancttggt	tggatncgaa	gcnataatct	ncntttctgc	ttggtggaca	gcaccantna	600
ctgtnnanct	ttagnccntg	gtcctcntgg	gttgnncttg	aacctaatcn	ccnntcaact	660
gggacaaggt	aantngccnt	cctttnaatt	cccnanctn	ccccctgggt	tggggttttn	720
cncnctecta	ccccagaaan	nccgtgttcc	cccccaacta	ggggccnaaa	ccnnttnttc	780
cacaacctn	ccccacccac	gggttcngnt	ggttng			816

<210> 15

<211> 783

<212> DNA

<213> Homo sapien

<220>

<221> misc\_feature

<222> (1)...(783)

<223> n = A,T,C or G

<400> 15

ccaaggcctg	ggcaggcata	nacttgaagg	tacaaccccc	ggaacccctg	gtgctgaagg	60
atgtggaaaa	cacagattgg	cgctactgc	ggggtgacac	ggatgtcagg	gtagagagga	120
agagcccaaa	ccaggtggaa	ctgtggggac	tcaagggaang	cacctacctg	ttccagctga	180
cagtgcactag	ctcagaccac	ccagaggaca	cgccaacgt	cacagtcact	gtgctgtcca	240
ccaagcagac	agaagactac	tgctcgcac	ccaacaangt	gggtcgcctg	cggggctctt	300
tccacgcctg	gtactatgac	cccacggagc	agatctgcaa	gagtttcgtt	tatggaggct	360
gtttgggcaa	caagaacaac	taccttcggg	aagaagagt	cattctancc	tgtcnggggtg	420
tgcaaggtgg	gcctttgana	ngcanctctg	gggtcangc	gactttcccc	cagggccctt	480
ccatggaaa	gcgccatcca	ntgttctctg	gcacctgtca	gcccacccag	ttccgctgca	540
ncaatggctg	ctgcacacac	antttcctng	aattgtgaca	acacccccca	ntgcccccaa	600
ccctcccaac	aaagcttccc	tgtnnaaaaa	tacnccantt	ggcttttnac	aaacncccg	660
cnctccntt	ttccccnntn	aacaaagggc	ntngentttt	gaactgccc	aaccnnggaa	720
ctnccnngg	aaaaantncc	ccccctgggt	cctnnaancc	cctccncaaa	antncccc	780
ccc						783

<210> 16  
 <211> 801  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(801)  
 <223> n = A,T,C or G

<400> 16

gccccaatte	cagctgccac	accacccacg	gtgactgcat	tagttcggat	gtcatacaaa	60
agctgattga	agcaaccctc	tactttttgg	togtgagcct	tttgcttgg	gcaggtttca	120
ttggctgtgt	tggtgacgtt	gtcattgcaa	cagaatgggg	gaaaggcact	gttctctttg	180
aagtaggggtg	agtcctcaaa	atccgtatag	ttggtgaagc	cacagcactt	gagccctttc	240
atgggtgggtg	tccacacttg	agtgaagtct	tcctgggaac	cataatcttt	cttcatggca	300
ggactacca	gcaacgtcag	gaagtgtctc	gccattgtgg	tgtacaccaa	ggcgaccaca	360
gcagctgcaa	cctcagcaat	gaagatgagg	aggaggatga	agaagaacgt	cncgagggca	420
cacttgetct	ccgtcttagc	accatagcag	cccangaaac	caagagcaaa	gaccacaacg	480
cengctgcga	atgaaagaaa	ntaccacagt	tgacaaaactg	catggccact	ggacgacagt	540
tgccccgaan	atcttcagaa	aagggtatgc	ccatcgattg	aacacccana	tgccactgc	600
cnacagggtg	gcncnncn	gaaagaatga	gccattgaag	aaggatcnc	ntgggtcttaa	660
tgaactgaaa	ccntgcatgg	tgccccctgt	tcagggtctt	tggcagtgaa	ttctganaaa	720
aaggaaacng	ntnagcccc	ccaaangana	aaacaccccc	gggtgttgcc	ctgaattggc	780
ggccaaggan	ccctgccccn	g				801

<210> 17  
 <211> 740  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(740)  
 <223> n = A,T,C or G

<400> 17

gtgagagcca	ggcgtccctc	tgctgcccac	ctcagtgcca	acacccggga	gctgttttgt	60
cctttgtgga	gcctcagcag	ttccctcttt	cagaactcac	tgccaagagc	cctgaacagg	120
agccaccatg	cagtgtctca	gcttcattaa	gaccatgatg	atcctcttca	atttgctcat	180
ctttctgtgt	ggtgcagccc	tggtggcagt	gggcattctg	gtgtcaatcg	atggggcatc	240
ctttctgaag	atcttcgggc	cactgtcgtc	cagtgccatg	cagtttgtca	acgtgggcta	300

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cttcctcacc gcagccggcg ttgtggtctt tgcctcttggg ttccctgggct gctatggtgc 360
taagacggag agcaagtgtg ccctcgtgac gttcttcttc atccctcctcc tcattctcat 420
tgctgaagtt gcagctgctg tggcgccctt ggtgtacacc acaatggctg aaccattcct 480
gacgttgctg gtantgctg ccatcaanaa agattatggg ttcccaggaa aaattcactc 540
aantntggaa caccnccatg aaaagggctc caatttctgn tggcttcccc aactataccg 600
gaattttgaa agantcnccc tacttccaaa aaaaaanant tgcctttncc ccnttctgt 660
tgcaatgaaa acntcccaan acngccaatn aaaacctgcc cnncaaaaa ggntcncaaa 720
caaaaaaant nnaagggttn

```

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<210> 18
<211> 802
<212> DNA
<213> Homo sapien

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<220>
<221> misc_feature
<222> (1)...(802)
<223> n = A,T,C or G

```

```

<400> 18
ccgctggttg cgctgggtcca gngnagccac gaagcacgtc agcatacaca gctcaatca 60
caaggtcttc cagctgccgc acattacgca gggcaagagc ctccagcaac actgcatatg 120
ggatacactt tacttttagca gccagggtga caactgagag gtgtcgaagc ttattcttct 180
gagcctctgt tagtgaggga agattccggg ctccagctaa gtatgcagcg tatgtcccat 240
aagcaaacac tgtgagcagc cggaaggtag aggcaaagtc actctcagcc agctctctaa 300
cattgggcat gtccagcagt tctccaaaca cgtagacacc agnggcctcc agcacctgat 360
ggatgagtgt ggccagcgct gcccccttgg ccgacttggc taggagcaga aattgctcct 420
ggttctgccc tgtaaccttc acttccgcac tcatactgc actgagtgtg ggggacttgg 480
gtcaggatg tccagagacg tggttccgcc ccctcnctta atgacaccgn ccanncaacc 540
gtcggctccc gccagantng ttcgtcgtnc ctgggtcagg gtctgctggc cnetacttgc 600
aancttcgtc nggccccatg aattcaccnc accggaactn gtangatcca ctnttctat 660
aaccggncgc caccgcnnnt ggaactccac tcttnttncc tttacttgag ggttaaggtc 720
acccttnncc ttaccttggg tcaaaccntn ccntgtgtcg anatingtnaa tcnngnccna 780
tnccancnc atangaagcc ng
802

```

```

<210> 19
<211> 731
<212> DNA
<213> Homo sapien

```

```

<220>
<221> misc_feature
<222> (1)...(731)
<223> n = A,T,C or G

```

```

<400> 19
cnaagcttcc aggtnacggg ccgnaancc tgaccenagg tancanaang cagnncgagg 60
gagcccaccg tcacngngng gngtctttat nggagggggc ggagccacat cnetggacnt 120
cntgacccca actcccnc nncantgca gtgatgagtg cagaactgaa ggtnacgtgg 180
caggaaccaa gancaaannc tgctcnntc caagtcggcn nagggggcgg ggctggccac 240
gencatecnt cnagtgtgn aaagccccnn cctgtctact tgtttgaga acngcnnnga 300
catgcccagn gttanataac nggcnagag tnannttggc tctcccttcc ggctgcgan 360
cngntntgct tagnggacat aacctgacta cttaactgaa ccnngaate tncnccct 420
ccactaagct cagaacaaaa aacttcgaca ccactcantt gtcacctgnc tgctcaagta 480
aagtgtaccc catncccaat gnttgetnga ngctctgnc tgcnttangt tcggtcctgg 540
gaagacctat caattnaagc tatgtttctg actgcctctt gctccctgna acaancnacc 600
cnnnntcca agggggggnc ggcccccaat ccccccaacc ntnaattnan tttancccn 660
ccccnggcc cggccttita cnancntenn nnaacnggna aaaccnnngc tttncccaac 720

```



nnaatecnc t

731

<210> 20  
 <211> 754  
 <212> DNA  
 <213> Homo sapien  
  
 <220>  
 <221> misc\_feature  
 <222> (1)...(754)  
 <223> n = A,T,C or G

<400> 20  
 tttttttttt tttttttttt taaaaacccc ctccattnaa tgnaaacttc cgaaattgtc 60  
 caacccccctc ntccaaatnn centttccgg gnggggggttc caaacccaan ttannttttg 120  
 annttaaatt aaatnttntt tggnggnna ancnaatgt nangaaagt naaccanta 180  
 tnancttnaa tncctggaaa cngtngntt ccaaaaatnt ttaacctta antccctcg 240  
 aaatngttna nggaaaaccc aantttctnt aaggttgttt gaaggntnaa tnaaaanccc 300  
 nnccaattgt ttttngccac gectgaatta attggnnttc gntgttttcc nttaaaanaa 360  
 gggnancccc gggtantnaa tcccccnnc cccaattata ceganttttt ttngaattgg 420  
 gancccnccg gaattaacgg ggnnnntccc tnttgggggg cnggncccc cccntcggg 480  
 gggtngggnc aggncnaat tgtttaaggg tccgaaaaat cctccnaga aaaaaanctc 540  
 ccaggntgag nntngggttt ncccccccc canggccct ctcgnanagt tgggggttgg 600  
 ggggcctggg attttntttt cectnttnc tcccccccc cngggganag aggttngnt 660  
 ttgntcnnc ggccccnccn aagancttn ceganttnan ttaaatcent gcctnggcga 720  
 agtccnttgn agggntaaan ggccccctnn cggg 754

<210> 21  
 <211> 755  
 <212> DNA  
 <213> Homo sapien  
  
 <220>  
 <221> misc\_feature  
 <222> (1)...(755)  
 <223> n = A,T,C or G

<400> 21  
 atcancat gacccnaac nngggacnc tcancggnc nnncnacnc cgccnatca 60  
 nngtnagnnc actncnnttn natcacccc cncnactac gcccnananc cnacgccta 120  
 nncanattnc actganngcg cganngan ngagaaanct nataccanag ncaccanacn 180  
 ccagctgtcc nanaangcct nnnatacngg nnnatccaat ntgnancctc cnaagtattt 240  
 nncnncanac gatatttctn anccgattac centcccccc tancctctcc cccccaacna 300  
 cgaaggcnc ggncnaagg nngcncncc ccgctagntc cccncaagt cncncncta 360  
 aactcanccn nattacncc ttcttgagta tcaactcccc aatctcacc tactcaactc 420  
 aaaaanaton gatacaaaat aatncaagcc tgnttatnac actntgactg ggtctctatt 480  
 ttagnggtcc ntnaanctc ctaatacttc cagtctncc tcnccaattt ccnaanggct 540  
 ctttngaca gcatnttttg gtcccnntt gggttcttan ngaattgcc ttctnngaac 600  
 gggctctct tttcttcgg ttancctggg ttcnccggc cagttattat ttcctntttt 660  
 aaattctnc cntttanttt tggcttcna aacccccggc cttgaaaaac gcccctggt 720  
 aabaggttgt ttganaaaa ttttgtttt gtcc 755

<210> 22  
 <211> 849  
 <212> DNA  
 <213> Homo sapien  
  
 <220>

<221> misc\_feature  
 <222> (1)...(849)  
 <223> n = A,T,C or G

<400> 22  
 tttttttttt tttttangtg tngtcgtgca ggtagaggct tactacaant gtgaanacgt 60  
 acgctnngan taangcgacc cgantttctag gannnccect aaaatcanac tgtgaagatn 120  
 atcctgnnna cggaanggtc accggnngat nntgctaggg tgneenctcc cannnenttn 180  
 cataactcng nggccctgcc caccacette ggcggeccng ngnccgggcc cgggtcattn 240  
 gnnttaaccn cactnngcna nccgtttccn nccccnncng acccnggcga tccgggggtnc 300  
 tctgtcttcc cctgnagncn anaaantggg ccccggnccc ctttaccctt nnacaagcca 360  
 cngccnteta nccnngccc cccctccant nngggggact gccnanngt ccggttncng 420  
 nnaccccnmn gggtnccctg gttgtcgant cnaccgnang ccanggattc cnaaggaagg 480  
 tgcgttnttg gccctaccc ttcgctnccg nncacccttc ccgacnanga nccgtcccgc 540  
 cncnncgng cctcncctcg caacaccgc nctentcngt nccggnnccc cccacccgc 600  
 nccctcncnc ngncgnancn ctcncnccc gtctcannca ccaccccgcc ccgccaggcc 660  
 ntcancacn ggngacnng nagenennte gncgcgcgn gcgncccct cgcncngaa 720  
 ctncntcngg ccantnncgc tcaancenna cnaaacgcgc ctgcgcggcc cgnagegncc 780  
 nccctcncga gtccctccgn ctcccnacc angnnttcn cgaggacaen nnaccccgcc 840  
 nncangcgg 849

<210> 23  
 <211> 872  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(872)  
 <223> n = A,T,C or G

<400> 23  
 ggcgaacta tacttegetc gnactcgtgc gctcgcctc tcttttctc cgcaaccatg 60  
 tctgacnanc cegattnggc ngatatchan aagntcganc agtccaaact gantaacaca 120  
 cacacnncan aganaaatcc nctgccttcc anagtanaen attgaacnng agaaccangc 180  
 nggcgaatcg taatnaggcg tgcgcgcga atntgtcncc gtttatttnn ccagctcnc 240  
 ctncncccc tacttctttn nagctgtcnn accctngtn cgnaccccc naggtcggga 300  
 tgggggtttnn nntgaccgng cnnccctcc cccntccat nacganccnc ccgcaccacc 360  
 nanngcncgc nccccgnnet cttegcencc ctgtcctntn cccctgtngc ctggcnngn 420  
 accgcattga cctcgcenn ctncnngaaa ncnanacgt ccgggttggn annancgtg 480  
 tgggnnngcg tctgcncgc gttccttcn ncncttcca ccatcttct tacngggctc 540  
 cncgcenctc tcnncacnc cctgggaagc tntcctntgc ccccttnac tccccctt 600  
 cgnctgncc cgnccccacc ntcatttnca nacgntcttc acaannnct ggnntnctcc 660  
 cnancngcn gtcancnag ggaaggngg ggnncennng nttgacgtg ngngangtc 720  
 cgaanantcc tcnccntcan cctaccctt cgggcgnnet ctngttnc aacttancaa 780  
 ntctcccccg ngngcnctc tcagcctcnc cnccecnct ctctgcantg tctctgctc 840  
 tnaccnntac gantnttcn cncctctt cc 872

<210> 24  
 <211> 815  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(815)  
 <223> n = A,T,C or G

```

<400> 24
gcattgcaagc ttgagttatc tatagngtca cctaaatanc ttggcntaat catggctenta      60
nctgncctcc tgggtcaaat gtatacnaaa tanatatgaa tctnatntga caagannnga      120
tctncatta gtaacaantg tnnigtccat cctgtongan canattccca tnnattncgn      180
cgcattcnch gencantatn taatngggaa ntcnnntnnn ncaccnncat ctatcntncc      240
genccttgac tggagagat ggatnanttc tnnntgacc nacatgttca tcttgattn      300
aanancccc cgcngnccac cgggtngnng cnagcchntc ccaagacctc ctgtggaggt      360
aacctgcgtc agannccatc aacntgggaa acccgchnc angtnnaagt ngnnncanan      420
gatcccgtec aggnntnacc atcccttenc agcgccccct ttngtgcctt anagnnagc      480
gtgtccnanc cnetcaacat ganacgcgcc agnccanccg caattnggca caatgtcgnc      540
gaacccccca gggggantna tncaaanccc caggattgtc cnencangaa atcccnanc      600
ccnccctac cennctttgg gacngtgacc aantcccgga gtncacgtcc ggcngnctc      660
ccccaccggt nncntgggg ggggtgaantc cngnntcanc cngncgaggn ntcgnaagga      720
accggnctn ggncgaanng ancnntenga agnccnct cgtataaacc cccctcncca      780
nccnncngnt agntcccccc cngggtnccg aangg      815

```

```

<210> 25
<211> 775
<212> DNA
<213> Homo sapien

```

```

<220>
<221> misc_feature
<222> (1)...(775)
<223> n = A,T,C or G

```

```

<400> 25
ccgagatgtc tgcctccgtg gccttagctg tgcctgcgct actctctctt tctggcctgg      60
aggctatcca ggcgtactca aagattcagg tttactcacg tcatccagca gagaatggaa      120
agtcaaaattt cctgaattgc tatgtgtctg ggtttcatcc atccgacatt gaanttgaact      180
tactgaagaa tgganagaga attgaaaaag tggagcatte agacttgtct ttcagcaagg      240
actggctctt ctatctontg tactacactg aattcacccc cactgaaaaa gatgagtatg      300
cctgccgtgt gaaccatgtg actttgtcac agcccaagat agttaagtgg gatcgagaca      360
tqlaagcagn cncatggaa gtttgaagat gcgcatttg gattggatga attccaaatt      420
ctgcttgctt gcnttttaat antgatatgc ntatacacc taccctttat gnceccaaat      480
tgtagggggt acatnantgt tcnctnngga catgatcttc ctttataant cncncttcg      540
aattgccgt cncnctnng ngaatgttcc cnaaaccag gttggctccc ccaggtncc      600
tcctacggaa ggccctgggc cnccttncaa ggttggggga accnaaaatt tcnctntgc      660
cncnccncca cncctttgng nncncanttt ggaaccttc cnattcccc ttggctcnaa      720
nccttnncta anaaaacttn aaancgtngc naaantttt acttcccccc ttacc      775

```

```

<210> 26
<211> 820
<212> DNA
<213> Homo sapien

```

```

<220>
<221> misc_feature
<222> (1)...(820)
<223> n = A,T,C or G

```

```

<400> 26
anattantac agtgtaatat tttcccagag gtgtgtanag ggaacggggc ctagaggcat      60
ccanagata ncttatanca acagtgtttt gaccaagagc tgctgggcac atttcctgca      120
gaaaagggtg cgggtcccat cactcctcct ctccatagc catcccagag ggggtgagtag      180
ccatcangcc ttccgtggga gggagtcang gaaacaacan accacagagc anacagacca      240
nttatgacca tgggctggag cgagcctctt cctgnaccg ggggtggcana nganagccta      300
nctgaggggt cacactataa acgttaacga ccnagatnan cactgcttc aagtgcacc      360

```

ttcctacctg	acnaccagng	accnnnaact	gengcctggg	gacagencgtg	ggancagcta	420
acnnagcaact	cacctgcccc	cccatggcgg	tnegentccc	tggtcctgnc	aagggaagct	480
ccctgttgga	attncgggga	naccaaggga	nccccctect	ccanctgtga	aggaaaaann	540
gatggaattt	tncccttccg	gcnntcccc	tcttccttta	cacgccccct	nnactctntc	600
tccctctntt	ntcctgncnc	acttttnacc	ccnnnatttc	ccttnattga	tcggannctn	660
ganattccac	tnnccctnc	cntcnatcng	naanacnaaa	nactntctna	ccnnggggat	720
gggnccctcg	ntcatcctct	ctttttcnct	accnccnntt	ctttgcctct	ccttnngatca	780
tccaacntc	gntggccntn	ccccccnnn	tccttttccc			820

<210> 27  
 <211> 818  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(818)  
 <223> n = A,T,C or G

<400> 27	
tctgggtgat	ggcctcttcc
tgtttcttct	ccgagcccca
ctgcggtatg	tgtgacggac
ctgctgagca	cttccgcccc
tcggcctcca	gggttctgct
ttcttctgct	cccttccctg
gatctcagtt	tccctcncct
tatnaccnan	tggnctgtnc
ntcccttccc	anttcnnnna
ctcctttgcc	ctnaccangg
ctgntnnccc	cncctcncnt
tnnctcttcn	ngntctgnaa
cnnntgnang	tnatttnnnn
cccncccccc	ngnattaagg
	cctccnntct
	ccggccnc
	60
	120
	180
	240
	300
	360
	420
	480
	540
	600
	660
	720
	780
	818

<210> 28  
 <211> 731  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(731)  
 <223> n = A,T,C or G

<400> 28	
aggaagggcg	gagggatatt
tcccaacatg	anggtgnngt
gattnaaccc	cattgtatgg
ntanattcct	gtnaatcgga
attnctccc	gtagtgcat
actaaagntt	naagtgggan
tnnnttnect	tgccctntg
nnngcgnnc	tgaaannnnc
cgtttcncat	naaggcactt
nggttcnct	acgctnnntg
gnaatgggta	gggncttntc
tctcnacccc	cccccttttt
	caatcccanc
	ggcnaatggg
	gtctccccnn
	cgangggggg
	60
	120
	180
	240
	300
	360
	420
	480
	540
	600
	660
	720

nnnnccannc c

731

<210> 29  
 <211> 822  
 <212> DNA  
 <213> Homo sapien  
  
 <220>  
 <221> misc\_feature  
 <222> (1)...(822)  
 <223> n = A,T,C or G

<400> 29  
 actagtccag tgtgggtggaa ttccattgtg ttggggncnc ttctatgant antnttagat 60  
 cgetcanacc tcacancctc ccnaccnangc ctataangaa nannaataga nctgtncnnt 120  
 atntntacnc tcatanncct cnnnaccac tccctcttaa ccntactgt gcctatngcn 180  
 tnnctantct ntgcgcctn cnanccaccn gtggggcnac cncnngnatt ctcnatctcc 240  
 tcnccatntn gcctananta ngtnccatac ctataccctac nccaatgcta nnnctaancn 300  
 tccatnantt annntaacta ccactgaent ngactttcnc atnanctcct aatttgaatc 360  
 tactctgact cccacngcct annnattagc ancttcccc nacnatntct caaccaaatc 420  
 ntcaacaacc tatctanctg ttcnccaacc nttncctcgg atccccnnac aacccccctc 480  
 ccaaataccc nccaactgac nccatacccn caccatcccg gcaagccnan ggncatttan 540  
 ccactggaat cacnatngga naaaaaaac ccnaactctc tancncnnat ctccctaana 600  
 aatnctcctn naatttactn ncantnccat caancccaen tgaaacnnaa cccctgtttt 660  
 tanatccctt ctttcgaaaa ccnacccttt annncccaac ctttnggggc ccccnctnc 720  
 cnaatgaag gncncccaat cnangaaacg nccntgaaaa ancnaggcna anannntccg 780  
 canatcctat cccttanttn ggggnccctt nccnggggcc cc 822

<210> 30  
 <211> 787  
 <212> DNA  
 <213> Homo sapien  
  
 <220>  
 <221> misc\_feature  
 <222> (1)...(787)  
 <223> n = A,T,C or G

<400> 30  
 cggcgcgctg ctctggcaca tgctcctga atggcatcaa aagtgatgga ctgcccattg 60  
 ctagagaaga ccttctctcc tactgtcatt atggagccct gcagactgag ggctcccctt 120  
 gtctgcagga tttgatgtct gaagtctgtg agtgtggctt ggagctcctc atctacatna 180  
 gotggaagcc ctggaggggc tctctcgcca gcctccccct tctctccacg ctctccangg 240  
 acaccagggg ctccaggcag cccattattc ccagnangac atgggtgttc tccacgcgga 300  
 cccatggggc ctgnaaggcc agggctctct ttgacaccat ctctcccgtc ctgcctggca 360  
 ggccgtggga tccactantt ctanaacggg cgccaccnec gtgggagctc cagcttttgt 420  
 tcccnttaat gaaggttaat tgcnccgttg gcgtaatcat nggtcanaac tntttcctgt 480  
 gtgaaattgt ttntccctc ncnattccnc ncnacatacn aacccggaan cataaagtgt 540  
 taaagcctgg gggtnccctn nngaattnaac tnaactcaat taattgcgtt ggctcatggc 600  
 ccgctttccn ttcnngaaaa ctgtcntccc ctgcnttntt gaatcggcca ccccccnggg 660  
 aaaagcgggt tgcnttttng ggggntcctt ccncttcccc cctcnctaan cctnccgect 720  
 cggctgttnc nggtngcggg gaangggnat nnnctccnc naagggggng agnnngntat 780  
 ccccaaa 822

<210> 31  
 <211> 799  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(799)  
 <223> n = A,T,C or G

<400> 31

tttttttttt	tttttttggc	gatgctactg	tttaattgca	ggaggtggg	gtgtgtgtac	60
catgtaccag	ggctattaga	agcaagaagg	aaggagggag	ggcagagcgc	cctgctgagc	120
aacaaaggac	tctgcagcc	ttctctgtct	gtctcttggc	gcaggcacat	ggggaggcct	180
cccgcagggt	gggggccacc	agtcacggg	tgggagcact	acanggggtg	ggagtgggtg	240
gtggctggtr	cnaatggcct	gncacanatc	cctacgattc	ttgacacctg	gatttcacca	300
ggggaccttc	tgtttcccca	nggnaacttc	ntnnatctcn	aaagaacaca	actgtttctt	360
cngcanttct	ggctgttcat	ggaaagcaca	ggtgtccnat	ttnggctggg	acttgggtaca	420
tatggttccg	gcccacctct	cccntcnaaa	aagtaattca	cccccccccn	ccntctnttg	480
cctggggcct	taantaccca	caccggaact	canttantta	ttcatcttng	gntgggcttg	540
ntnatcnccn	cctgaangcg	ccaagttgaa	aggccacgcc	gtncccnctc	cccatagnan	600
ntttttnent	cantctaatgc	ccccccnggc	aacnatecaa	tcccccccn	tggggggccc	660
agcccanggc	cccgcgctcg	ggnnncengn	cnegnantec	ccaggntctc	ccantcngnc	720
ccnnngcncc	cccgcacgca	gaacanaagg	ntngagccnc	cgcannnnnn	nggttnncnac	780
ctcgccccc	ccnccgngg					799

<210> 32  
 <211> 789  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(789)  
 <223> n = A,T,C or G

<400> 32

tttttttttt	tttttttttt	tttttttttt	tttttttttt	tttttttttt	tttttttttt	60
ttttncnag	ggcagggtta	ttgacaacct	cnccgggacac	aancaggctg	gggacaggac	120
ggcaacaggc	tccggcgggc	gcggcggcgg	ccctacctgc	ggtaccaaata	ntgcagcctc	180
cgtcccgcgt	tgatnttcc	ctgcagctgc	aggatgccnt	aaaacagggc	ctcgccentn	240
ggtgggcacc	ctgggatttn	aatttccacg	ggcacaatgc	ggtcgcancc	cctcaccacc	300
nattaggaat	agtggtnnta	ccnccncccg	ttggcncaact	cccnttggaa	accacttntc	360
gcggtctcgg	catctggtct	taaaccttgc	aaacnctggg	gccctctttt	tggttantnt	420
ncnngccaca	atcatnactc	agactggcnc	gggctggccc	caaaaaancn	ccccaaaacc	480
ggncatgtc	ttncgggggt	tgctgcnatn	tncatcacct	cccgggcnca	ncaggncaac	540
ccaaaagtgc	ttngggcccn	caaaaaanct	ccgggggggnc	ccagtttcaa	caaagtcate	600
ccccttggcc	cccaaactct	ccccccgntt	ncgtgggtttg	ggaacccacg	cctctnnctt	660
tggnnnggcaa	gntggntccc	ccttcggggc	cccgggtgggc	ccnncctcaa	ngaaaacncc	720
ntcctnnnca	ccatccccc	nngnnacgnc	tancaangna	tccctttttt	tanaaacggg	780
ccccccncc						789

<210> 33  
 <211> 793  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(793)  
 <223> n = A,T,C or G

&lt;400&gt; 33

gacagaacat	gttgatgggt	ggagcacctt	tctatacgac	ttacaggaca	gcagatgggg	60
aattcattggc	tgttggagca	atanaacccc	agttctacga	gctgctgac	aaaggacttg	120
gactaaagtc	tgatgaactt	cccaatcaga	tgagcatgga	tgattggcca	gaaatgaana	180
agaagtttgc	agatgtattt	gcaaagaaga	cgaaggcaga	gtggtgtcaa	atctttgacg	240
gcacagatgc	ctgtgtgact	cgggttctga	cttttgagga	ggttgttcat	catgatcaca	300
acaangaaog	gggctcgttt	atcaccantg	aggagcagga	cgtgagcccc	cgccttgcac	360
ctctgctgtt	aaacaccccc	gccatccctt	ctttcaaaaag	ggatccacta	cttctagagc	420
ggncgccacc	gcggtggagc	tccagctttt	gttcccttta	gtgaggggta	attgcgcgct	480
tqqcgtaatc	atgggtcatan	ctgtttcctg	tgtgaaattg	ttatccgctc	acaattccac	540
acaaacatac	anccggaagc	atnaaatttt	aaagcctggn	ggtngcctaa	tgantgaact	600
naetcacatt	aattggcttt	gcgctcactg	cccgctttcc	agtcgggaaa	acctgtcctt	660
gccagctgcc	nttaatgaat	cnggccaccc	cccggggaaa	aggcngtttg	cttnttgggg	720
cgencttccc	gctttctcgc	ttcctgaant	ccttcccccc	ggtctttcgg	cttgcggcna	780
acqgtatena	cct					793

&lt;210&gt; 34

&lt;211&gt; 756

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; (1)...(756)

&lt;223&gt; n = A,T,C or G

&lt;400&gt; 34

gcgcgacccg	gcattgtacga	gcaactcaag	ggcgagtggga	accgtaaaag	ccccaatctt	60
anccaagtgcg	gggaanagct	gggtcgactc	aagctagtto	ttctggagct	caacttcttg	120
ccaaccacag	ggaccaagct	gaccaaaacag	cagctaatte	tgccccgtga	catactggag	180
atcggggccc	aatggagcat	cctacgcaan	gacatccctt	ccttcgagcg	ctacatggcc	240
cagctcaaat	gctactactt	tgattacaan	gagcagctcc	cagagtcagc	ctatatgcac	300
caactcttgg	gcctcaacct	cctcttcttg	ctgtcccaga	accgggtggc	tgantnccac	360
ccqganttgg	anccgctgcc	tgcaccaanga	catacanacc	aatgtctaca	tcnaccacca	420
gtgtccttga	gcaatactga	tgganggcag	ctaccncaaa	gtnttctctg	ccnagggtaa	480
cataccccgc	cgaagctac	accttcttca	ttgacatcct	gctcgacact	atcagggatg	540
aaatcgcnng	ggttgctcca	gaaaggctnc	aanaanatec	ttttcncctga	aggccccggg	600
atnnctagt	nctagaatcg	gcccgcacac	gcggtgganc	ctccaacctt	tcgtnccctt	660
ctactgaggg	ttnattgccg	cccttgccgt	tatcatggtc	acnccngttn	cctgtgttga	720
aattnttaac	ccccacaaat	tccacgcena	catnng			756

&lt;210&gt; 35

&lt;211&gt; 834

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; (1)...(834)

&lt;223&gt; n = A,T,C or G

&lt;400&gt; 35

gggaatctct	anatenacct	gnatgcatgg	ttgtcggtgt	ggtcgctgtc	gatgaanatg	60
gacaggatct	tgccttggaa	gctctcggtt	gctgtnttta	agttgctcag	tctgccgtca	120
taatcagaca	cncctttggg	caaaaaacan	caggatntga	gtcttgattt	caactccaat	180
aatcttcngg	gctgtctgct	cgggtgaactc	gatgaacnang	ggcagctggg	tgtgtntgat	240
gaantccanc	angttctcct	tggtgacctc	cccttcaaaq	ttgttcgggc	cttcatcaaa	300
attctnnaan	angannancc	canctttgtc	gagctgggnat	ttgganaaca	cgtcactggt	360

ggaaactgat	cccaaagtgt	atgtcatcca	tgccctctgc	tgccctgcaaa	aaacttgctt	420
ggcncaaata	cgactcccn	tccttgaaag	aagccnatca	cacccccctc	cctggactcc	480
nncaangact	ctnccgctnc	cccntccnng	cagggttggt	ggcannccgg	gccccgtgcg	540
ttcttcagcc	agttcacnat	nttcatcage	ccctctgcc	gctgttntat	tccttggggg	600
<b>ggaanccgtc</b>	<b>tctcccttcc</b>	<b>tgaannaact</b>	<b>ttgaccgtng</b>	<b>gaatagccgc</b>	<b>gcntcncnt</b>	<b>660</b>
acntnctggg	cggggttcaa	antccctecn	ttgncnntcn	cctcgggcca	ttctggattt	720
nccnaacttt	ttccttcccc	cncctccnng	ngtttgntt	tttcatnggg	ccccaaactct	780
gctnttgcc	antcccttgg	gggentntan	cncctcctnt	ggtccctng	ggcc	834

&lt;210&gt; 36

&lt;211&gt; 814

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; (1)...(814)

&lt;223&gt; n = A,T,C or G

&lt;400&gt; 36

cgngcgttt	ccngccgcgc	cccgtttcca	tgacnaagge	tccttcang	ttaaatacnn	60
cctagnaaac	attaatgggt	tgctctacta	atacatcata	cnaaccagta	agcctgcccc	120
naacgccaac	tcaggccatt	cctaccaaag	gaagaaagge	tggtctctcc	acccccgtga	180
ggaaaggcct	gccttgtaag	acaccacaat	ncggctgaat	ctnaagtctt	gtgttttact	240
aatggaaaaa	aaaaataaac	aanagggtttt	gttctcatgg	ctgcccaccg	cagcctggca	300
ctaaaaacanc	ccagcgctca	cttctgcttg	ganaaatatt	ctttgctctt	ttggacatca	360
ggcttgatgg	tatcaactgcc	acntttccac	ccagctgggc	ncccttcccc	catntttgtc	420
antganctgg	aaggcctgaa	ncttagtctc	caaaagtctc	ngcccacaag	accggccacc	480
agggggangtc	ntttncagtg	gatctgccaa	anantaccen	tatcatcnnt	gaataaaaag	540
gcccctgaac	ganatgcttc	cancancctt	taagacccat	aatcctngaa	ccatgggtgcc	600
cttcgggtct	gatecnaaag	gaatgttctt	gggtcccant	ccctcctttg	ttnccttaagt	660
tgtnttggaac	ccttgctngn	atnacccaan	tganatcccc	ngaagcacc	tncccttggc	720
atttganttt	cntaaattct	ctgccttaac	nctgaaagca	cnattccctn	ggcncnnaaa	780
gnggaactca	agaagggtctn	ngaaaaacca	cncn			814

&lt;210&gt; 37

&lt;211&gt; 760

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; (1)...(760)

&lt;223&gt; n = A,T,C or G

&lt;400&gt; 37

gcatgctgct	cttctcctcaaa	gttggttcttg	ttgccataac	aaccaccata	ggtaaagcgg	60
gcgcagtggt	cgctgaaggg	gttgtagtac	cagcgcgagg	tgctctcctt	gcagagtctt	120
gtgtctggca	ggtccacgca	atgccctttg	tactggggga	aatggatgcg	ctggagctcg	180
tcaanccac	tcgtgtatatt	ttcacangca	gcctcctccg	aagctccggg	gcagttgggg	240
gtgtcgtcac	actccactaa	actgtcgatn	cancagccca	ttgctgcagc	ggaactgggt	300
gggctgacag	gtgccagaac	acactggatn	ggcctttcca	tggaagggcc	tgggggaaat	360
cncctnancc	caaaactgct	ctcaaaggcc	accttgaca	ccccgacagg	ctagaaatgc	420
actcttcttc	ccaaaggtag	ttgttcttgt	tgcccaagca	ncctccanca	aaccaaanc	480
ttgcaaaatc	tgctccgtgg	gggtcatnnn	taccanggtt	ggggaaanaa	acccggcngn	540
ganccnctt	gtttgaatgc	naaggnaata	atcctcctgt	cttgcttggg	tggaanagca	600
caattgaact	gttaacnttg	ggccnggttc	cncctnggtg	gtctgaaact	aatcacgcgc	660
actggaaaaa	ggtangtgcc	ttccttgaat	tcccaaantt	ccctngntt	tgggtntttt	720



ctcctctncc ctaaaaatcg tnttcccccc centanggcg

760

<210> 38  
 <211> 724  
 <212> DNA  
 <213> Homo sapien  
 <220>  
 <221> misc\_feature  
 <222> (1)...(724)  
 <223> n = A,T,C or G

<400> 38  
 tttttttttt tttttttttt tttttttttt ttttttaaaaa cccctcccat tgaatgaaaa 60  
 ctccnnaaat tgtccaaccc cctcnnecaa atnnccattt ccgggggggg gttccaaacc 120  
 caaattaatt ttgganttta aattaaatnt tnattnngggg aanaanccaa atgtnaagaa 180  
 aatttaaccc attatnaact taaatnccn gaaaccntg gnttccaaaa atttttaacc 240  
 cttaaatccc tccgaaattg ntaanggaaa accaaattcn cctaaggctn tttgaagggt 300  
 ngatttaaac ccccttnant tnttttnacc cnnngctnaa ntattnngnt tccggtgttt 360  
 tccntntaan cntnggtaac tcccgnataa gaannnccct aanccaatta aaccgaattt 420  
 tttttgaatt ggaaattccn ngggaattna ccgggggttt tccnttttg gggccatncc 480  
 ccncctttcg ggggttggn ntaggttgaa ttttttnang nccccaaaaa ncccccaana 540  
 aaaaaactcc caagnnttaa ttngaatttc ccccttccca ggcccttttg gaaaggnggg 600  
 tttntggggg ccngggantt cnttccccc ttncncccc cccccnggt aaanggttat 660  
 ngnttttgt ttttgggccc cttnanggac cttccggatn gaaattaaat ccccggnccg 720  
 gccg 724

<210> 39  
 <211> 751  
 <212> DNA  
 <213> Homo sapien  
 <220>  
 <221> misc\_feature  
 <222> (1)...(751)  
 <223> n = A,T,C or G

<400> 39  
 tttttttttt tttttctttg ctacacattta atttttattt tgattttttt taatgctgca 60  
 caacacaata tttatttcat ttgtttcttt tatttcattt tatttgtttg ctgctgctgt 120  
 tttatttatt tttactgaaa gtgagaggga acttttgttg ccttttttcc tttttctgta 180  
 ggccgcctta agctttctaa atttggaaca tctaagcaag ctgaanggaa aagggggttt 240  
 cgcaaaatca ctggggggaa nggaaagggt gctttgttaa tcatgcccta tgggtgggtga 300  
 ttaactgctt gtacaattac ntttcacttt taattaattg tgcnaangc ttttaattana 360  
 cttgggggtt cccctcccan accaaccnccn ctgacaaaaa gtgcngccc tcaaatnatg 420  
 tcccgcnnt enttgaaaca cacngcngaa ngttctcatt ntcccnccn caggtnaaaa 480  
 tgaagggtta ccatntttta cncacctcc acntggcnnn gcctgaatcc tcnaaaanccn 540  
 cctcaanccn aattnctnng ccccggtcnc gcntnngtcc cncccgggct ccgggaantn 600  
 cccccnga annccntnnc naacnaaatt ccgaaaatat tccnntcnc tcaattcccc 660  
 cnnagactnt cctcnncnccn cncaattttc tttntntcac gaacnccnnc cnaaaatgn 720  
 nnnnccctc cncntngtcn naatcnccan c 751

<210> 40  
 <211> 753  
 <212> DNA  
 <213> Homo sapien

<220>

<221> misc\_feature  
 <222> (1)...(753)  
 <223> n = A,T,C or G

<400> 40  
 gtggtatttt ctgtaagatc aggtgttcct ccctcgtagg tttagaggaa acaccctcat 60  
 agatgaaaac ccccccgaga cagcagcaact gcaactgccca agcagccggg gtaggagggg 120  
 cgccctatgc acagctgggc ccttgagaca gcagggttc gatgtcaggc tcgatgtcaa 180  
 tggctctggaa ggggcggctg tacctgcgta ggggcacacc gtcaggggccc accaggaact 240  
 tctcaaagtt ccaggcaacn tcgttgcgac acaccggaga ccagggtgatn agcttggggg 300  
 cggtcataa cgggtggcg tcgtcgtgg gagctggcag ggcctccgc aggaaggcna 360  
 ataaaagggtg cggcccgca cgttcact cgcacttctc naanaccatg angttgggct 420  
 cnaaccacc accannccgg acttccttga nggaattccc aaatctcttc gntcttgggc 480  
 ttctnctgat gccctanctg gttgccnngn atgccaancc nccccaancc ccgggggtcct 540  
 aaanccaccn cctcctcctt tcatctgggt tnttntcccc ggacctgggt tectetcaag 600  
 ggancaccata tctnaccan tactcacct nccccccnt gnnaccanc cttctanngn 660  
 tccccnccg nctctggcc cntcaaan gcttncacna cctgggtctg ccttcccccc 720  
 tccccctatc gnacccnctn ttgtctcan tnt 753

<210> 41  
 <211> 341  
 <212> DNA  
 <213> Homo sapien

<400> 41  
 actatatcca tcacaacaga catgcttcat cccatagact tcttgacata gcttcaaagt 60  
 agtgaaccca tccttgattt atatacatat atgttctcag tattttggga gcctttccac 120  
 ttcttttaaac cttgttcatt atgaacactg aaaataggaa tttgtgaaga gttaaaaagt 180  
 tatagcttgt ttacgtagta agtttttgaa gtctacattc aatccagaca cttagttgag 240  
 tgttaaactg tgatttttaa aaaatatcat ttgagaatat tctttcagag gtattttcat 300  
 ttttactttt tgattaattg tgttttatat attagggtag t 341

<210> 42  
 <211> 101  
 <212> DNA  
 <213> Homo sapien

<400> 42  
 acttactgaa tttagtcttg tgctcttccct tatttagtgt tgtatcataa atactttgat 60  
 gtttcaaaca ttctaaataa ataattttca gtggcttcat a 101

<210> 43  
 <211> 305  
 <212> DNA  
 <213> Homo sapien

<400> 43  
 acatctttgt tacagtctaa gatgtgttct taaatcacca ttccttctg gtcctcaccc 60  
 tccagggtgg tctcacactg taattagagc tattgaggag tctttacagc aaattaagat 120  
 tcagatgcct tgctaagtct agagttctag agttatgtt cagaaagtct aagaaaccca 180  
 cctcttgaga ggtcagtaaa gaggacttaa ttttcatat ctacaaaatg accacaggat 240  
 tggatacaga acgagagtta tcttgataa ctcagagctg agtacctgcc cgggggcccgc 300  
 tcgaa 305

<210> 44  
 <211> 852  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(852)  
 <223> n = A,T,C or G

<400> 44  
 acataaatat cagagaaaag tagtctttga aatatttacg tccaggagtt ctttgtttct 60  
 gattatttgg tgtgtgtttt ggtttgtgtc caaagtattg gcagcttcag ttttcatttt 120  
 ctctccatcc tcgggcattc ttcccaaatt tatataccag tcttcgtcca tccacacgct 180  
 ncagaatttc tctttttag tagtatctca tagctcggct gagcttttca taggtcatgc 240  
 tgcgtgtgtt cttcttttta ccccatagct gagccactgc ctctgatttc aagaacctga 300  
 agacgccctc agatcggtct tcccatttta ttaatcctgg gttcttgtct gggttcaaga 360  
 ggatgtcgcg gatgaattcc cataagttag tccctctcgg gttgtgcttt ttggtgtggc 420  
 acttggcagg ggggtcttgc tcttttttca tatcagggtga ctctgcaaca ggaaggtgac 480  
 tgggtggtgt catggagatc tgagcccggc agaaagtatt gctgtccaac aaatctactg 540  
 tgctaccata gttggtgtca tataaatagt tctngtcttt ccagggtgtc atgatggaag 600  
 gctcagtttg ttcagtcttg acaatgacat tgtgtgtgga ctggaacagg tcactactgc 660  
 actggccggt ccaacttcaga tgcgtcaagt tgcgttagag gagntgcccc gccgtccctg 720  
 ccgccgggt gaactcctgc aaactcatgc tgcaaagggt ctgccggtg atgtcgaact 780  
 cntgaaaagg gatacaattg gcatccagct ggttggtgtc caggaggtga tggagccact 840  
 cccacacctg gt 852

<210> 45  
 <211> 234  
 <212> DNA  
 <213> Homo sapien

<400> 45  
 acaacagacc cttgctcgtt aacgacctca tgctcatcaa gttggacgaa tccgtgtccg 60  
 agtctgacac catccggagc atcagcattg ctctgcagtg cctaccgcg gggaaactctt 120  
 gccctgtttc tggctggggt ctgctggcga acggcagaat gccaccgtg ctgcagtgcg 180  
 taaactgtgc ggtggtgtct gaggaggtct gcagtaagct ctatgaccg ctgt 234

<210> 46  
 <211> 590  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(590)  
 <223> n = A,T,C or G

<400> 46  
 acttttttatt taaatgttta taaggcagat ctatgagaat gatagaaaac atggtgtgta 60  
 atttgatagc aatatttttg agattacaga gtttttagta ttaccaatta cacagttaaa 120  
 aagaagataa tatattccaa gcanatacaa aatatctaata gaaagatcaa ggcaggaaaa 180  
 tgantataac taattgacaa tggaaaatca attttaattg gaattgcaca ttatccttta 240  
 aaagctttca aaanaaanaa ttattgcagt ctanttaatt caaacagtg taaatggtat 300  
 caggataaan aactgaaggg canaaaagaat taattttcac ttcattgtaac ncacccanat 360  
 ttacaatggc ttaaattgcan ggaaaaagca gtggaagtag ggaagtantc aaggtctttc 420  
 tggctctctaa tctgccttac tctttgggtg tggctttgat cctctggaga cagctgccag 480  
 ggctcctgtt atatccacaa tcccagcagc aagatgaagg gatgaaaaag gacacatgct 540  
 gccctccttt gaggagactt catctcactg gccaaactc agtcacatgt 590

<210> 47  
 <211> 774

<212> DNA  
<213> Homo sapien

<220>  
<221> misc\_feature  
<222> (1)...(774)  
<223> n = A,T,C or G

<400> 47  
acaagggggc ataatgaagg agtggggana gatttttaaag aaggaaaaaa aacgaggccc 60  
tgaacagaat ttctctgnac aacggggcctt caaaataatt ttcttgggga gggtcaagac 120  
gcttcaactgc ttgaaactta aatggatgtg ggacanaatt ttctgtaatg accctgaggg 180  
cattacagac gggactctgg gaggaaggat aaacagaaaag gggacaaaag ctaatcccaa 240  
aacatcaaag aaaggaagggt ggcgtcatac ctcccagcct acacagttct ccagggtctct 300  
cctcatccct ggaggacgac agtggaggaa caactgacca tgtccccagg ctctgtgtg 360  
ctggctcctg gtcttcagcc cccagctctg gaagcccacc ctctgtgat cctgcgtggc 420  
ccacactcct tgaacacaca tccccagggtt atattcctgg acatggctga acctcctatt 480  
cctacttccg agatgccttg ctccctgcag cctgtcaaaa tcccaactcac cctccaaacc 540  
acggcatggg aagcctttct gacttgccctg attactccag catcttggaa caatccctga 600  
ttcccactc cttagaggca agataggggtg gtttaagagta gggctggacc acttggagcc 660  
aggtgtctgg cttcaaattn tggctcattt acgagctatg ggaccttggg caagtnatct 720  
tcactttctat gggentcatt ttgttctacc tgcaaaatgg gggataataa tagt 774

<210> 48  
<211> 124  
<212> DNA  
<213> Homo sapien

<220>  
<221> misc\_feature  
<222> (1)...(124)  
<223> n = A,T,C or G

<400> 48  
canaaattga aattttataa aaaggcattt ttctottata tocataaaat gatataattt 60  
ttgcaantat anaaatgtgt cataaattat aatgttcctt aattacagct caacgcaact 120  
tggt 124

<210> 49  
<211> 147  
<212> DNA  
<213> Homo sapien

<220>  
<221> misc\_feature  
<222> (1)...(147)  
<223> n = A,T,C or G

<400> 49  
gccgatgcta ctattttatt gcaggaggtg ggggtgtttt tattattctc tcaacagctt 60  
tgtggctaca ggtgggtgtct gactgcatna aaaanttttt tacgggtgat tgcaaaaatt 120  
ttagggcacc catatcccaa gcantgt 147

<210> 50  
<211> 107  
<212> DNA  
<213> Homo sapien

<400> 50  
 acattaaatt aataaaagga ctgttggggt tctgctaaaa cacatggctt gatatatgtg 60  
 atggtttgag gttaggagga gttaggcata tgttttggga gaggggt 107

<210> 51  
 <211> 204  
 <212> DNA  
 <213> Homo sapien

<400> 51  
 gtctaggaa gtctagggga cacacgactc tgggggtcacg ggcccgacac acttgcaagg 60  
 ggggaaggaa aggcagagaa gtgacaccgt cagggggaaa tgacagaaag gaaaatcaag 120  
 gctttgcaag gtcagaaagg ggactcaggg ctccaccac agccctgcc cacttggcca 180  
 cctccctttt gggaccagca atgt 204

<210> 52  
 <211> 491  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(491)  
 <223> n = A,T,C or G

<400> 52  
 acaaagataa catitatctt ataacaaaaa tttgatagtt ttaaagggtta gtatttgtga 60  
 gggatatttt caaaagacta aagagataac tcaggtaaaa agttagaaat gtataaaaca 120  
 ccatcagaca ggttttttaa aaacaacata ttacaaaatt agacaatcat ccttaaaaaa 180  
 aaaacttctt gtatcaattt cttttgttca aaatgactga cttaantatt tttaaatatt 240  
 tcanaaacac ttctcaaaaa attttcaana tggtagcttt canatgtnc ctcagtccca 300  
 atgttgttca gataaataaa tctcgtgaga acttaccacc caccacaagc tttctggggc 360  
 atgaaacagt gtcttttctt tnccttttct ttttttttt ttacaggcac agaaactcat 420  
 caattttatt tggataacaa agggtctcca aattatattg aaaaataaat ccaagttaat 480  
 atcaactctt t 491

<210> 53  
 <211> 484  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(484)  
 <223> n = A,T,C or G

<400> 53  
 acataattta gcagggctaa ttaccataag atgctattta ttaanaggtn tatgatctga 60  
 gtattaacag ttgctgaagt ttggatattt tatgcagcat tttctttttg ctttgataac 120  
 actacagaac ccttaaggac actgaaaatt agtaagttaa gttcagaaac attagctgct 180  
 caatcaaate tctacataac actatagtaa ttaaaacggt aaaaaaaagt gttgaaatct 240  
 qcactagtat anaccgctcc tgtcaggata anactgcttt ggaacagaaa gggaaaaanc 300  
 agctttgant ttctttgtgc tgatangagg aaaggctgaa ttaccttggt gcctctccct 360  
 aatgattggc aggtcnggta aatnccaaaa catattccaa ctcaacactt cttttccncg 420  
 fancttgant ctgtgtattc caggancagg cggatggaat gggccagccc nccgatgttc 480  
 fant 484

<210> 54

<211> 151  
 <212> DNA  
 <213> Homo sapien

<400> 54  
 actaaacctc gtgcttgtga actccatata gaaaacggtg ccatccctga acacggctgg 60  
 ccactgggta tactgctgac aaccgcaaca acaaaaacac aaatccttgg cactggctag 120  
 tctatgtcct ctcaagtgcc tttttgtttg t 151

<210> 55  
 <211> 91  
 <212> DNA  
 <213> Homo sapien

<400> 55  
 acctggcttg tctccgggtg gttcccggtg cccccacgg tccccagaac ggacactttc 60  
 gccctccagt ggatactcga gccaaagtgg t 91

<210> 56  
 <211> 133  
 <212> DNA  
 <213> Homo sapien

<400> 56  
 ggcggatgtg cgttggttat atacaaatat gtcattttat gtaagggact tgagtatact 60  
 tggatttttg gtatctgtgg gttgggggga cgggccagga accaataccc catggatacc 120  
 aaggggacaac tgt 133

<210> 57  
 <211> 147  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(147)  
 <223> n = A,T,C or G

<400> 57  
 actctggaga acctgagccg ctgctccgcc tctgggatga ggtgatgcan gcngtggcgc 60  
 gactgggagc tgagcccttc cctttgcgcc tgcctcagag gattgttgcc gacntgcana 120  
 tctcantggg ctggatncat gcagggt 147

<210> 58  
 <211> 198  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(198)  
 <223> n = A,T,C or G

<400> 58  
 acagggatat aggtttnaag ttattgtnat tgtaaaatac attgaatttt ctgtatactc 60  
 tgattacata catttatcct ttaaaaaaga tgtaaatctt aatttttatg ccatctatta 120  
 atttaccat gagttacctt gtaaatgaga agtcatgata gcactgaatt ttaactagtt 180  
 ttgacttcta agtttgggt 198

<210> 59  
 <211> 330  
 <212> DNA  
 <213> Homo sapien

<400> 59  
 ccaacaaatg ggttgtgagg aagtcttata agcaaaactg gtgatggcta ctgaaaagat 60  
 ccattgaaaa ttatcattaa tgattttaaa tgacaagtta tcaaaaactc actcaatttt 120  
 cactgtgct agcttgctaa aatgggagtt aactctagag caaatatagt atcttctgaa 180  
 tcaagtcatt aaatgacaaa gccaggacct acaggtggtt tccagacttt ccagaccag 240  
 cagaaggaat ctattttatc acatggatct ccgtctgtgc tcaaaatacc taatgatatt 300  
 ttctgtcttt attggacttc tttgaagagt 330

<210> 60  
 <211> 175  
 <212> DNA  
 <213> Homo sapien

<400> 60  
 accgtgggtg ccttctacat tctgacggc tcttcacca acatctggtt ctacttcggc 60  
 gtctgggct ccttctctt catctcctc cagctgggtg tgctcatcga ctttgccgac 120  
 tcttggaaac agcgggtggc gggcaaggcc gaggagtgcg attcccggtc ctggt 175

<210> 61  
 <211> 154  
 <212> DNA  
 <213> Homo sapien

<400> 61  
 acccaacttt tctcctgtg agcagtctgg acttctcact gctacatgat gaggggtgagt 60  
 gggtgttgc cttcaacagt atctcctcct ttccggatct gctgagccgg acagcagtgc 120  
 tgaactgcac agccccgggg ctccacattg ctgt 154

<210> 62  
 <211> 30  
 <212> DNA  
 <213> Homo sapien

<400> 62  
 cgctcgagcc ctatagttag tcgtattaga 30

<210> 63  
 <211> 89  
 <212> DNA  
 <213> Homo sapien

<400> 63  
 acaagtcatt tcagcaccct ttgctcttca aaactgacca tcttttatat ttaatgcttc 60  
 ctgtatgaat aaaaatggtt atgtcaagt 89

<210> 64  
 <211> 97  
 <212> DNA  
 <213> Homo sapien

<400> 64  
 accggagtaa ctgagtcggg acgtgaatc tgaatccacc aataaataaa gggtctgcag 60

aatcagtgca tccaggattg gtccttggat ctggggg

97

<210> 65  
 <211> 377  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(377)  
 <223> n = A,T,C or G

<400> 65  
 acaacaanaa ntcccttctt taggccaactg atggaaacct ggaacccccct tttgatggca 60  
 gcatggcgtc ctaggccttg acacagcggc tggggtttgg gctntcccaa accgcacacc 120  
 ccaaccctgg tctaccacaa nttctggcta tgggctgtct ctgccactga acatcagggt 180  
 tcggtcataa natgaaatcc caanggggac agaggtcagt agaggaagct caatgagaaa 240  
 ggtgctgttt gctcagccag aaaacagctg cctggcattc gccgctgaac tatgaaccog 300  
 tgggggtgaa ctaccccan gaggaatcat gcctgggcga tgcaanggtg ccaacaggag 360  
 gggcgggagg agcatgt 377

<210> 66  
 <211> 305  
 <212> DNA  
 <213> Homo sapien

<400> 66  
 acgcctttcc ctcagaattc agggaagaga ctgtcgctg ccttctctcog ttgttgogtg 60  
 agaaccctg tgcccttcc caccatatcc accctcgctc catctttgaa ctcaaacacg 120  
 aggaactaac tgcaccctgg tctctctccc agtccccagt tcacctcca tccctcacct 180  
 tctctcactc taagggatat caacactgcc cagcacaggg gccctgaatt tatgtggttt 240  
 ttatatattt ttttaataaga tgcactttat gtcatttttt aataaagtct gaagaattac 300  
 tgttt 305

<210> 67  
 <211> 385  
 <212> DNA  
 <213> Homo sapien

<400> 67  
 actacacaca ctccacttgc ccttgtgaga cactttgtcc cagcacttta ggaatgctga 60  
 ggtcggacca gccacatctc atgtgcaaga ttgccagca gacatcaggt ctgagagttc 120  
 cccttttaaa aaaggggact tgccttaaaaa agaagtctag ccacgattgt gtagagcagc 180  
 tgtgctgtgc tggagattca cttttgagag agttctctc tgagacctga tctttagagg 240  
 ctgggcagtc ttgcacatga gatggggctg gtctgatctc agcactcctt agtctgcttg 300  
 cctctcccag ggccccagcc tggccacacc tgcttacagg gcactctcag atgccatac 360  
 catagtttct gtgctagtgg accgt 385

<210> 68  
 <211> 73  
 <212> DNA  
 <213> Homo sapien

<400> 68  
 acttaaccag atatatTTTT accccagatg gggatattct ttgtaaaaaa tgaaaataaa 60  
 gtttttttaa tgg 73

<210> 69



<211> 536  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(536)  
 <223> n = A,T,C or G

<400> 69  
 actagctccag tgtggtggaa ttccattgtg ttgggggctc tcaccctcct ctcctgcagc 60  
 tccagctttg tgccttgcct ctgaggagac catggcccag catctgagta ccttgcctgt 120  
 cctgctggcc accctagctg tggccctggc ctggagcccc aaggaggagg ataggataat 180  
 ccgggtggc atctataacg cagacctcaa tgatgagtgg gtacagcgtg ccttcactt 240  
 cgcctcagc gagtataaca aggccaccaa agatgactac tacagacgtc cgtgcgggt 300  
 actaagaacc aggcacacga cgttggggg ggtgaattac ttcttcgacg tagaggtggg 360  
 ccgaaccata tgaaccaagt cccagcccaa ctggacacc tgtgccttcc atgaacagcc 420  
 agaactgcag aagaaacagt tgtgctcttt cgagatctac gaagtccct ggggagaaca 480  
 gaangtccct ggttgaactc caggtgtcaa gaaatccan ggatctgttg ccaggc 536

<210> 70  
 <211> 477  
 <212> DNA  
 <213> Homo sapien

<400> 70  
 atgaccccta acaggggccc tctcagccct cctaattgacc tccggcctag ccatgtgatt 60  
 tcaactccac tccataacgc tctcataact aggcctacta accaacacac taaccatata 120  
 ccaatgatgg cgcgaltgaa cagagaaaag cacataccaa ggccaccaca caccacctgt 180  
 ccaaaaaggc ctctgatacg ggataatcct atttattacc tcagaagttt tttcttcgc 240  
 agggattttt ctgagccttt taccactcca gcctagcccc taccocccaa ctaggagggc 300  
 actggccccc aacaggcctc accccgctaa atccctaga agtcccaact ctaaacacat 360  
 ccgtattact cgcctcagga gtatcaatca cctgagctca ccatagtcta atagaaaaca 420  
 accgaaacca aattattcaa agcactgctt attacaattt tactgggtct ctatttt 477

<210> 71  
 <211> 533  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(533)  
 <223> n = A,T,C or G

<400> 71  
 agagctatag gtacagtgtg atctcagctt tgcaaacaca tttctacat agatagtact 60  
 aggtattaat agatatgtaa agaaagaaat cacaccatta ataatggtaa gattgggtta 120  
 tgtgatttta gtggtatttt tggcaccctt atatatgttt tccaaacttt cagcagtgat 180  
 attatttcca taacttaaaa agtgagtttg aaaaagaaaa tctccagcaa gcctctcatt 240  
 taaataaagg tttgtcctct ttaaaaatac agcaatatgt gactttttta aaaagctgtc 300  
 aaataggtgt gaccctacta ataattatta gaaatacatt taaaaacatc gagtacctca 360  
 agtcagtttg ccttgaaaaa tatcaaatat aactcttaga gaaatgtaca taaaagaatg 420  
 ctctgtaatt ttggagtang aggttccctc ctcaattttg tattttttaa aagtacatgg 480  
 taaaaaaaaa aattcacacac agtatataag gctgtaaaat gaagaattct gcc 533

<210> 72  
 <211> 511

<212> DNA  
<213> Homo sapien

<220>  
<221> misc\_feature  
<222> (1)...(511)  
<223> n = A,T,C or G

<400> 72  
tattacggaa aaacacacca cataattcaa ctancaaaga anactgcttc agggcgtgta 60  
aaatgaaagg cttccaggca gttatctgat taaagaacac taaaagaggg acaaggctaa 120  
aagccgcagg atgtctacac tatancaggc gctatttggg ttggctggag gagctgtgga 180  
aaacatggan agattggtgc tgganacgc cgtggctatt cctcattgtt attacanaagt 240  
gaggttctct gtgtgccac tggtttgaaa accgttctnc aataatgata gaatagtaca 300  
cacatgagaa ctgaaatggc ccaaacccag aaagaaaagcc caactagatc ctcagaanac 360  
gcttctaggg acaataaccg atgaagaaaa gatggcctcc ttgtgcccc gtctgttatg 420  
atttctctcc attgcagcna naaacccgtt cttctaagca aacncagggtg atgatggcna 480  
aaatacacc cctcttgaag naccnggagg a 511

<210> 73  
<211> 499  
<212> DNA  
<213> Homo sapien

<220>  
<221> misc\_feature  
<222> (1)...(499)  
<223> n = A,T,C or G

<400> 73  
cagtgccagc actggtgcca gtaccagtac caataacagt gccagtgcc ggtccagcac 60  
cagtgggtgc ttccagtgtg gtgccagcct gaccgccact ctcacatttg ggctcttcgc 120  
tggccttggt ggagctggtg ccagcaccag tggcagctct ggtgcctgtg gtttctecta 180  
caagtgagat tttagatatt gttaatcctg ccagctcttc tcttcaagcc aggggtgcac 240  
ctcagaaacc tactcaacac agcactctag gcagccacta tcaatcaatt gaagttgaca 300  
ctctgcatta aatctatttg ccatttctga aaaaaaaaaa aaaaaaaggg cggccgctcg 360  
antctagagg gcccgtttaa acccgctgat cagcctcgac tgtgccttct anttgccagc 420  
catctgttgt ttgcccctcc cccgntgcct tccttgaccc tggaaagtgc cactcccact 480  
gtcctttcct aantaaaat 499

<210> 74  
<211> 537  
<212> DNA  
<213> Homo sapien

<220>  
<221> misc\_feature  
<222> (1)...(537)  
<223> n = A,T,C or G

<400> 74  
tttcatagga gaacacactg aggagatact tgaagaatth ggattcagcc gcgaagagat 60  
ttatcagctt aactcagata aaatcattga aagtaataag gtaaaagcta gtctctaact 120  
tccaggccca cggctcaagt gaatttgaat actgcattta cagtgtagag taacacataa 180  
cattgtatgc atggaaacat ggaggaacag tattacagtg tccaccact ctaatcaaga 240  
aaagaattac agactctgat tctacagtga tgattgaatt ctaaaaatgg taatcattag 300  
ggcttttgat ttataanact ttgggtactt atactaaatt atggtagtta tactgccttc 360  
cagtttgctt gatataattg ttgatattaa gattcttgac ttatattttg aatgggttct 420

```
actgaaaaan gaatgatata ttcttgaaga catcgatata cttttattta cactcttgat 480
tctacaatgt agaaaatgaa ggaaatgccc caaattgcat ggtgataaaa gtcocgt 537
```

```
<210> 75
<211> 467
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(467)
<223> n = A,T,C or G
```

```
<400> 75
caaanacaat tgttcaaaag atgcaaataa tacactactg ctgcagctca caaacacctc 60
tgcatattac acgtacctcc tctgtctcct caagtagtgt ggtctatttt gccatcatca 120
cctgtgtgtc gcttagaaga acggctttct gctgcaangg agagaaatca taacagacgg 180
tggcacaagg aggccatctt ttctcctcgc gttattgtcc ctagaagcgt cttctgagga 240
tctagtggg ctttctttct gggtttgggc catttcantt ctcatgtgtg tactattcta 300
tcattattgt ataacgggtt tcaaaccngt gggcacncag agaacctcac tctgtaataa 360
caatgaggaa tagccacggg gatctccagc accaaatctc tccatgttnt tccagagctc 420
ctccagccaa cccaaatagc cgctgctatn gtgtagaaca tccctgn 467
```

```
<210> 76
<211> 400
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(400)
<223> n = A,T,C or G
```

```
<400> 76
aagctgacag cattcgggcc gagatgtctc gtcocgtggc cttagctgtg ctgcgcctac 60
tctctcttcc tggcctggag gctatccagc gtactccaaa gattcagggt tactcacgtc 120
atccagcaga gaattgaaa tcaaatttcc tgaattgcta tgtgtctggg ttcatccat 180
ccgacattga agttgactta ctgaagaatg gagagagaat tgaaaaagtg gagcattcag 240
acttgtcttt cagcaaggac tggctcttct atctcttgta ctacactgaa ttcccccca 300
ctgaaaaaga tgagtatgcc tgccgtgtga accatgtgac tttgtcacag cccaagatng 360
ttnagtggga tctanacatg taagcagcan catgggaggt 400
```

```
<210> 77
<211> 248
<212> DNA
<213> Homo sapien
```

```
<400> 77
ctggagtgcc ttggtgtttc aagccctgc aggaagcaga atgcaccttc tgaggcacct 60
ccagctgcc cggcggggga tgcgaggtc ggagcaccct tgcccggctg tgattgctgc 120
caggcactgt tcatctcagc tttctgtcc ctttgcctcc ggcaagcgt tctgtgaaa 180
gttcatatct ggagcctgat gtcttaacga ataaaggctc catgctccac ccgaaaaaaa 240
aaaaaaaaa 248
```

```
<210> 78
<211> 201
<212> DNA
<213> Homo sapien
```

```

<400> 78
actagtccag tgtgggtggaa ttccattgtg ttggggcccaa cacaatggct acctttaaca      60
tcacccagac cccgccctgc ccgtagccca cgtgctgct aacgacagta tgatgcttac      120
tctgctactc ggaaactatt tttatgtaat taatgtatgc tttcttggtt ataaatgcct      180
gatttaaaaa aaaaaaaaaa a                                201

```

```

<210> 79
<211> 552
<212> DNA
<213> Homo sapien

```

```

<220>
<221> misc_feature
<222> (1)...(552)
<223> n = A,T,C or G

```

```

<400> 79
tccttttgtt aggtttttga gacaacccta gacctaaact gtgtcacaga cttctgaatg      60
tttaggcagt gctagtaatt tctctgtaat gattctgtta ttactttcct attctttatt      120
cctctttcct ctgaagatta atgaagttga aaattgaggt ggataaatac aaaaaggtag      180
tgtgatagta taagtatcta agtgcagatg aaagtgtggt atatatatcc attcaaaatt      240
atgcaagtta gtaattactc agggttaact aaattacttt aatatgctgt tgaacctact      300
ctgttccttg gctagaaaaa attataaaca ggactttggt agtttgggaa gccaaattga      360
taatattcta tgttctaaaa gttgggctat acataaanta tnaagaaata tgggaatttta      420
ttcccaggaa tatgggggtc atttatgaat antaccggg anagaagttt tgantnaaac      480
cngtttttgt taatacgtta atatgtcctn aatnaacaag gcntgactta tttccaaaaa      540
aaaaaaaaaa aa                                          552

```

```

<210> 80
<211> 476
<212> DNA
<213> Homo sapien

```

```

<220>
<221> misc_feature
<222> (1)...(476)
<223> n = A,T,C or G

```

```

<400> 80
acagggattt gagatgctaa ggccccagag atcgtttgat ccaaccctct tatttttcaga      60
ggggaaaaatg gggcctagaa gttacagagc atctagctgg tgcgtggca cccctggcct      120
cacacagact cccgagtagc tgggactaca ggcacacagt cactgaagca ggccctgttt      180
gcaattcacg ttgccacctc caacttaaac attcttcata tgtgatgtcc ttagtcacta      240
agggttaaact ttcccaccca gaaaaggcaa cttagataaa atcttagagt actttcatac      300
tcttctaagt cctcttcag cctcactttg agtcctcctt gggggttgat aggaantntc      360
tcttggtttt ctcaataaaa tctctatcca tctcatgttt aatttggtac gcntaaaaat      420
gctgaaaaaa ttaaaatgtt ctggtttcnc tttaaaaaaa aaaaaaaaaa aaaaaa      476

```

```

<210> 81
<211> 232
<212> DNA
<213> Homo sapien

```

```

<220>
<221> misc_feature
<222> (1)...(232)
<223> n = A,T,C or G

```

```

<400> 81
tttttttttg tatgcctnctn ctgtggngtt attgttgetg ccaccctgga ggagcccagt      60
ttctttctgta tcttttctttt ctggggggtc ttcttggtc tgccctccca tteccagcct      120
ctcatcccca tctttgcaatt ttgctagggt tggaggcgt ttcttggtag cccctcagag      180
actcagtcag cgggaataag tcttaggggt ggggggtgtg gcaagccggc ct                232

```

```

<210> 82
<211> 383
<212> DNA
<213> Homo sapien

```

```

<220>
<221> misc_feature
<222> (1)...(383)
<223> n = A,T,C or G

```

```

<400> 82
aggcgggagc agaagctaaa gccaaagccc aagaagagtg gcagtgccag cactggtgcc      60
agtaccagta ccaataacat gccagtgccg gtgccagcac cagtgggtggc ttcagtgetg      120
gtgccagcct gaccgccact ctacattttg ggtctctgc tgcccttggg ggagctggtg      180
ccagcaccag tggcagctct ggtgctgtg gttctctcta caagtgagat tttagatatt      240
gttaatctg ccagctcttc tcttcaagcc aggggtgcac ctacagaaacc tactcaacac      300
agcactctng gcagccacta tcaatcaatt gaagttgaca ctctgcatta aatctatttg      360
ccatttcaaa aaaaaaaaaa aaa                383

```

```

<210> 83
<211> 494
<212> DNA
<213> Homo sapien

```

```

<220>
<221> misc_feature
<222> (1)...(494)
<223> n = A,T,C or G

```

```

<400> 83
acggaattgg gaccgctggc ttataagcga tcatgtcttc cagtattacc tcaacgagca      60
gggagatcga gtctatacgc tgaagaaatt tgaccgatg ggacaacaga cctgctcagc      120
ccatcctgct cggttctccc cagatgacaa atactctcga caccgaatca ccatcaagaa      180
acgcttcaag gtgtcatga ccagcaacc gcgccctgtc ctctgagggt ccttaaactg      240
atgtctttt tgccacctgt taccctcgg agactccgta accaaactct tcggactgtg      300
agccctgatg cctttttgcc agccatactc tttggcntcc agtctctcgt ggcgattgat      360
tatgcttggt tgaggcaatc atggtggcat caccatnaa gggaacacat ttganTTTTT      420
tttcncatat tttaaattac naccagaata nttcagaata aatgaattga aaaactctta      480
aaaaaaaaaa aaaa                          494

```

```

<210> 84
<211> 380
<212> DNA
<213> Homo sapien

```

```

<220>
<221> misc_feature
<222> (1)...(380)
<223> n = A,T,C or G

```

```

<400> 84

```

```

gctggtagcc tatggcgtgg ccacggangg gctcctgagg cacgggacag tgaattccca      60
agtatcctgc gccgcgtctt ctaccgtccc tacctgcaga tcttcgggca gattccccag      120
gaggacatgg acgtggccct catggagcac agcaactgct cgtcggagcc cggcttctgg      180
gcacaccctc ctgggggccc ggcgggcacc tgcgtctccc agtatgccaa ctggctggtg      240
gtgctgctcc tcgtcatctt cctgctcgtg gccaacatcc tgctgggtcac ttgctcattg      300
ccatgttcag ttacacattc ggcaaagtac agggcaacag cnatctctac tgggaaggcc      360
agcgttnccg cctcatccgg                                     380

```

```

<210> 85
<211> 481
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(481)
<223> n = A,T,C or G

```

```

<400> 85
gagttagctc ctccacaacc ttgatgaggt cgtctgcagt ggcctctcgc ttcataccgc      60
tnccatcgtc ataactgtagg tttgccacca cctcctgcat cttggggcgg ctaatatcca      120
ggaaactctc aatcaagtca ccgtcnatna aacctgtggtc tggttctgtc ttccgctcgg      180
tgtgaaagga tctccagaag gagtgtctga tcttccccac acttttgatg actttattga      240
gtcgattctg catgtccagc aggaggttgt accagctctc tgacagttag gtcaccagcc      300
ctatcatgcc ntgaacgtg ccgaagaaca ccgagccttg tgtggggggg gnagtctcac      360
ccagattctg cattaccaga nagccgtggc aaaaganatt gacaactcgc ccaggngaa      420
aaagaacacc tcttggaagt gctngccgct cctcgteent tggtggnngc gentnccttt      480
t                                                                481

```

```

<210> 86
<211> 472
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(472)
<223> n = A,T,C or G

```

```

<400> 86
aacatcttcc tgtataatgc tgtgtaatat cgatccgatn ttgtctgctg agaattcatt      60
acttgaaaaa gcaacttnaa gcctggacac tggattaaaa attcacaata tgcaacactt      120
taaacagtgt gtcaatctgc tcccttactt tgtcatcacc agtctgggaa taagggtatg      180
cctattcac acctgttaaa agggcgctaa gcatttttga ttcaacatct ttttttttga      240
cacaagtcgg aaaaaagcaa aagtaaacag ttnttaattt gttagccaat tcaactttctt      300
catgggacag agccatttga tttaaaaagc aaattgcata atattgagct ttgggagctg      360
atatntgagc ggaagantag cctttctact tcaccagaca caactccttt catattggga      420
tgttnacnaa agttatgtct cttacagatg ggatgctttt gtggcaattc tg                472

```

```

<210> 87
<211> 413
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(413)
<223> n = A,T,C or G

```

<400> 87  
 aaaaaaccagt atctctnaaa acaacctctc ataccttggtg gacctaatTT tgtgtgcgtg 60  
 tgtgtgtgcg cgcataattat atagacaggc acatcttttt tacttttgta aaagcttatg 120  
 cctctttggT atctatatct gtgaaagttt taatgatctg ccataatgtc ttggggacct 180  
 ttgtcttctg tgtaaattgg actagagaaa acacctatnt tatgagtcaa tctagttngt 240  
 ttatttcgac atgaaggaaa ttccagatn acaacaetna caaactctcc ctgactagg 300  
 ggggacaaaag aaaagcnaaa ctgaacatna gaaacaattn cctgggtgaga aattncataa 360  
 acagaaattg ggtngtatat tgaaanang catcatnaa acgttttttt ttt 413

<210> 88  
 <211> 448  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(448)  
 <223> n = A,T,C or G

<400> 88  
 cgcagcgggt cctctctatc tagctccagc ctctcgctg ccccaactcc cgcgtccgc 60  
 gtcttagccn accatggcgc ggccctgcg cgcccgctg ctcttctgtg ccactctggc 120  
 cgtggccctg gccgtgagcc cgcgggcgcg ctccagtcgc ggcaagccgc cgcgcctggt 180  
 gggaggccca tggacccgc gtggaagaag aaggtgtgcg gctgactg gactttgcgc 240  
 tggcnanta caacaaaccc gcaacnactt ttaccnagen cgcgtgcag gttgtgcgc 300  
 cccaancaaa ttgttactng gggtaantaa ttcttggaag ttgaacctg gccaaacng 360  
 tttaccagaa ccnagccaat tngaacaatt nccctccat aacagccct tttaaaaagg 420  
 gaancantcc tgntcttttc caaatTT 448

<210> 89  
 <211> 463  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(463)  
 <223> n = A,T,C or G

<400> 89  
 gaattttgtg cactggccac tgtgatggaa ccattgggccc aggatgcttt gagtttatca 60  
 ttagtgattc tgccaaagt ggtgttgtaa catgagtatg taaaatgtca aaaaattagc 120  
 agaggtctag gtctgcatat cagcagacag ttgtccgtg tattttgtag ccttgaagtt 180  
 ctcaagtaca agttnnttct gatgcgaagt tctnattoca gtgttttagt cctttgcac 240  
 tttnatgtn agacttgcc ctntnaaatt gctttgtnt tctgcaggta ctatctgtg 300  
 ttttaacaaaa tagaannact tctctgcttn gaanatttga atatcttaca tctnaaaatn 360  
 aattctctcc ccatannaaa acccangccc ttggganaat ttgaaaaang gntccttcnn 420  
 aattcnana anttcagtn tcatacaaca naacngganc ccc 463

<210> 90  
 <211> 400  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(400)

<223> n = A,T,C or G

<400> 90  
 agggattgaa ggtctnttnt actgtcggac tgttcancca ccaactctac aagttgctgt 60  
 cttccactca **ctgtctgtaa** **gcntnttaac** **ccagactgta** **tcttcataaa** **tagaacaaat** 120  
 tcttcaccag tcacatcttc taggaccttt ttggattcag ttagtataag ctcttccact 180  
 tcctttgtta agacttcctc tggtaaagtc ttaagttttg tagaaaggaa ttttaattgct 240  
 cgttctctaa caatgtcctc tccttgaagt atttggctga acaaccacc tnaagtcct 300  
 ttgtgcatcc attttaaata tacttaatag ggcattggtg cactagggtta aattctgcaa 360  
 gagtcatctg tctgcaaaag ttgcgttagt atatctgcca 400

<210> 91

<211> 480

<212> DNA

<213> Homo sapien

<220>

<221> misc\_feature

<222> (1)...(480)

<223> n = A,T,C or G

<400> 91  
 gagctcggat ccaataatct ttgtctgagg gcagcacaca tatncagtgc catggnaact 60  
 ggtctacccc acatgggagc agcatgccgt agntatataa ggctattccc tgagtcagac 120  
 atgcctcttt gactaccgtg tgccagtgcg ggtgattctc acacacctcc nncgcctctt 180  
 tgtggaaaaa ctggcaacttg nctggaacta gcaagacatc acttaciaat tcaccacaga 240  
 gacacttgaa aggtgtaaca aagcgactct tgcattgctt tttgtccctc cggcaccagt 300  
 tgtcaatact aaccgcgtgg tttgctcca tcacatttgt gatctgtagc tctggatata 360  
 tcctctgaca gtactgaaga acttcttctt ttgtttcaaa agcaactctt ggtgcctggt 420  
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<210> 92

<211> 477

<212> DNA

<213> Homo sapien

<220>

<221> misc\_feature

<222> (1)...(477)

<223> n = A,T,C or G

<400> 92  
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 gaaccttccg cctgttctct ggcgtcacct gcagctgctg ccgetnacac tcggcctcgg 360  
 accagcggac aaacggcgtt gaacagccgc acctcacgga tgcccantgt gtcgcgctcc 420  
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<210> 93

<211> 377

<212> DNA

<213> Homo sapien

<220>

<221> misc\_feature



<222> (1)...(377)

<223> n = A,T,C or G

<400> 93

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cgcttcaatg	cagaaccant	agtgggagca	ctgtgttttag	agttaagagt	gaacactgtn	180
tgattttact	tgggaatttc	ctctgtttata	tagcttttcc	caatgctaata	ttccaaacaa	240
caacaacaaa	ataacatgtt	tgcctgttina	gttgataaaa	agtangtgat	tctgtatnta	300
aaqaaaatat	tactgtttaca	tatactgctt	gcaanttctg	tattttattgg	tnctctggaa	360
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<210> 94

<211> 495

<212> DNA

<213> Homo sapien

<220>

<221> misc\_feature

<222> (1)...(495)

<223> n = A,T,C or G

<400> 94

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ccaaggaaag	accaccttct	ggggacatgg	gctggagggc	aggacctaga	ggcaccagg	180
gaaggcccca	ttccgggggt	gttcccagag	gaggaaggga	aggggctctg	tgtgcccccc	240
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tgcaagctca	ccaagggtccc	ctctcagtc	cttccctaca	ccctgaacgg	ncaactggccc	360
acaccacccc	agancancca	cccgccatgg	ggaatgttct	caaggaatcg	cngggcaacg	420
tggaactctng	tcccnnaagg	gggcagaatc	tccaatagan	gganngaacc	cttgcctnana	480
aaaaaaaaana	aaaaa					495

<210> 95

<211> 472

<212> DNA

<213> Homo sapien

<220>

<221> misc\_feature

<222> (1)...(472)

<223> n = A,T,C or G

<400> 95

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atcggcacaaa	tgtggagtgt	atgttctttt	cacagtaata	tatgcctttt	gtaacttcac	360
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<210> 96

<211> 476

<212> DNA

<213> Homo sapien

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; (1)...(476)

&lt;223&gt; n = A,T,C or G

&lt;400&gt; 96

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tgtgttagtc	tcaattccta	ccacactgag	ggagcctccc	aatcactat	attcttatct	360
gcaggtactc	ctccagaaaa	acngacaggg	caggcttgca	tgaaaaagtn	acatctgcgt	420
tacaaagtct	atcttctctca	nangtctgtn	aaggaacaat	ttaatcttct	agcttt	476

&lt;210&gt; 97

&lt;211&gt; 479

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; (1)...(479)

&lt;223&gt; n = A,T,C or G

&lt;400&gt; 97

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caatcgcaaa	tcaaaactca	caagtgtctca	tctgtttagt	atttagtgta	ataagactta	180
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atnnntttta	natcaaagta	ttttgtgttt	ggaantgtnn	aaatgaaatc	tgaatgtggg	420
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&lt;210&gt; 98

&lt;211&gt; 461

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 98

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ttacctggag	aaaagaggct	ttggctgggg	accatcccat	tgaaccttct	cttaaggact	360
ttaagaaaaa	ctaccacatg	ttgtgtatcc	tggtgccggc	cgtttatgaa	ctgaccaccc	420
tttgggaataa	tcttgacgct	cctgaacttg	ctcctctgcg	a		461

&lt;210&gt; 99

&lt;211&gt; 171

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 99

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<212> DNA  
<213> Homo sapien

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<210> 101  
<211> 405  
<212> DNA  
<213> Homo sapien

<400> 101  
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gatgatcagt acgaataccg aggcattatc tcatatcggt ggcca 405

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<211> 470  
<212> DNA  
<213> Homo sapien

<400> 102  
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lcaaaatcta aattattcaa attagccaaa tccttaccaa ataataccca aaaatcaaaa 180  
atatacttct ttcagcaaac ttgttacata aattaaaaaa atatatacgg ctgggtgtttt 240  
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ccgcaaagggt taaagggaac aacaaattct ttacaacac cattataaaa atcatatctc 360  
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ttttaaacca ttgtttgggc ccaacacaat ggaatcccc ctggactagt 470

<210> 103  
<211> 581  
<212> DNA  
<213> Homo sapien

<400> 103  
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ccatttttagt cactaaacga tatcaaagtg ccagaatgca aaaggtttgt gaacatttat 540

tcaaaagcta atataagata tttcacatac tcatctttct g 581

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 <211> 578  
 <212> DNA  
 <213> Homo sapien

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 <211> 538  
 <212> DNA  
 <213> Homo sapien

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<210> 106  
 <211> 473  
 <212> DNA  
 <213> Homo sapien

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<210> 107  
 <211> 1621  
 <212> DNA  
 <213> Homo sapien

<400> 107  
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&lt;210&gt; 108

&lt;211&gt; 382

&lt;212&gt; PRT

&lt;213&gt; Homo sapien

&lt;400&gt; 108

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Arg Val Asp Arg Pro Gly Ser Arg Tyr Asp Val Ser Arg Leu Gly Arg
35          40          45
Gly Lys Arg Ser Leu Val Leu Asp Leu Lys Gln Pro Arg Gly Ala Ala
50          55          60
Val Leu Arg Arg Leu Cys Lys Arg Ser Asp Val Leu Leu Glu Pro Phe
65          70          75          80
Arg Arg Gly Val Met Glu Lys Leu Gln Leu Gly Pro Glu Ile Leu Gln
85          90          95
Arg Glu Asn Pro Arg Leu Ile Tyr Ala Arg Leu Ser Gly Phe Gly Gln
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Ser Gly Ser Phe Cys Arg Leu Ala Gly His Asp Ile Asn Tyr Leu Ala
115         120         125
Leu Ser Gly Val Leu Ser Lys Ile Gly Arg Ser Gly Glu Asn Pro Tyr
130         135         140
Ala Pro Leu Asn Leu Leu Ala Asp Phe Ala Gly Gly Gly Leu Met Cys
145         150         155         160
Ala Leu Gly Ile Ile Met Ala Leu Phe Asp Arg Thr Arg Thr Asp Lys
165         170         175
Gly Gln Val Ile Asp Ala Asn Met Val Glu Gly Thr Ala Tyr Leu Ser
180         185         190
Ser Phe Leu Trp Lys Thr Gln Lys Ser Ser Leu Trp Glu Ala Pro Arg

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195		200		205
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Tyr Glu Leu Leu Ile Lys Gly Leu Gly Leu Lys Ser Asp Glu Leu Pro				
245	250	255		
Asn Gln Met Ser Met Asp Asp Trp Pro Glu Met Lys Lys Lys Phe Ala				
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Asp Val Phe Ala Lys Lys Thr Lys Ala Glu Trp Cys Gln Ile Phe Asp				
275	280	285		
Gly Thr Asp Ala Cys Val Thr Pro Val Leu Thr Phe Glu Glu Val Val				
290	295	300		
His His Asp His Asn Lys Glu Arg Gly Ser Phe Ile Thr Ser Glu Glu				
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Gln Asp Val Ser Pro Arg Pro Ala Pro Leu Leu Leu Asn Thr Pro Ala				
325	330	335		
Ile Pro Ser Phe Lys Arg Asp Pro Phe Ile Gly Glu His Thr Glu Glu				
340	345	350		
Ile Leu Glu Glu Phe Gly Phe Ser Arg Glu Glu Ile Tyr Gln Leu Asn				
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 <211> 1524  
 <212> DNA  
 <213> Homo sapien

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&lt;211&gt; 3410

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 110

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ctccctctca ctctctctag gactgggctg atgaaggcac tgcccaaaat ttccctacc      3060
cccaactttc cctaccccc aactttcccc accagctcca caaccctgtt tggagctact      3120
gcaggaccag aagcacaag tgcgggttcc caagcctttg tccatctcag ccccagagt      3180
atatctgtgc ttggggaatc tcacacagaa actcaggagc acccctgccc tgagctaagg

```

```

gaggtcttat ctctcagggg gggtttaagt gccgtttgca ataatgtcgt cttattttatt 3240
tagcggggtg aatattttat actgtaagtg agcaatcaga gtataatgtt tatggtgaca 3300
aaattaaagg ctttcttata tgtttaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 3360
aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaataaa aaaaaaaaaa 3410

```

<210> 111  
 <211> 1289  
 <212> DNA  
 <213> Homo sapien

```

<400> 111
agccaggcgt cctctgcct gccactcag tggcaacacc cgggagctgt tttgtccttt 60
gtggagcctc agcagttccc tctttcagaa ctcaactgcc agagccctga acaggagcca 120
ccatgcagtg cttcagcttc attaagacca tgatgatcct cttcaatttg ctcatcttcc 180
tgtgtggtgc agccctgttg gcagtgggca tctgggtgtc aatcgatggg gcaccccttc 240
tgaagatctt cgggccactg tgcgccagt ccattgcagtt tgtcaacgtg ggctacttcc 300
tcattgcagc cggcgttgtg gtctttgtct ttgggttccct gggctgctat ggtgctaaga 360
ctgagagcaa gtgtgccctc gtgacgttct tcttcactct cctcctcctc ttcattgtctg 420
agggttgtag tgcgtgtgtc gccttggtgt acaccacaat ggctgagcac ttcctgacgt 480
tgctggtagt gccctgccatc aagaaagatt atgggttcca ggaagacttc actcaagtgt 540
ggaacaccac catgaaaagg ctcaagtgtc gtggcttcac caactatacg gattttgagg 600
actcacccta cttcaaagag aacagtgcct tccccctatt ctggttgaat gacaacgtca 660
ccaacacagc caatgaaacc tgcaccaagc aaaaggctca cgaccaaaaa gtagagggtt 720
gcttcaatca gcttttgtat gacatccgaa ctaatgcagt caccgtgggt ggtgtggcag 780
ctggaattgg gggcctcgag ctggctgcca tgattgtgtc catgtatctg tactgcaatc 840
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accctggcaa gcagcagtgat ttggggggagg ggacaggatc taacaatgtc acttgggcca 960
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gtagccagtt ctgttgccca tccccccagt ctattaaacc cctgatatgc cccctaggcc 1140
tagtggtgat ccagtgctc tactggggga tgagagaaag gcattttata gcctgggcat 1200
aagtgaatc agcagagcct ctgggtggat gtgtagaagg cacttcaaaa tgcataaacc 1260
tggtacaatg ttaaaaaaaa aaaaaaaaaa
1289

```

<210> 112  
 <211> 315  
 <212> PRT  
 <213> Homo sapien

```

<400> 112
Met Val Phe Thr Val Arg Leu Leu His Ile Phe Thr Val Asn Lys Gln
1          5          10          15
Leu Gly Pro Lys Ile Val Ile Val Ser Lys Met Met Lys Asp Val Phe
20          25          30
Phe Phe Leu Phe Phe Leu Gly Val Trp Leu Val Ala Tyr Gly Val Ala
35          40          45
Thr Glu Gly Leu Leu Arg Pro Arg Asp Ser Asp Phe Pro Ser Ile Leu
50          55          60
Arg Arg Val Phe Tyr Arg Pro Tyr Leu Gln Ile Phe Gly Gln Ile Pro
65          70          75          80
Gln Glu Asp Met Asp Val Ala Leu Met Glu His Ser Asn Cys Ser Ser
85          90          95
Glu Pro Gly Phe Trp Ala His Pro Pro Gly Ala Gln Ala Gly Thr Cys
100         105         110
Val Ser Gln Tyr Ala Asn Trp Leu Val Val Leu Leu Val Ile Phe
115         120         125
Leu Leu Val Ala Asn Ile Leu Leu Val Asn Leu Leu Ile Ala Met Phe
130         135         140

```



Ser Tyr Thr Phe Gly Lys Val Gln Gly Asn Ser Asp Leu Tyr Trp Lys  
 145 150 155 160  
 Ala Gln Arg Tyr Arg Leu Ile Arg Glu Phe His Ser Arg Pro Ala Leu  
 165 170 175  
 Ala Pro Pro Phe Ile Val Ile Ser His Leu Arg Leu Leu Leu Arg Gln  
 180 185 190  
 Leu Cys Arg Arg Pro Arg Ser Pro Gln Pro Ser Ser Pro Ala Leu Glu  
 195 200 205  
 His Phe Arg Val Tyr Leu Ser Lys Glu Ala Glu Arg Lys Leu Leu Thr  
 210 215 220  
 Trp Glu Ser Val His Lys Glu Asn Phe Leu Leu Ala Arg Ala Arg Asp  
 225 230 235 240  
 Lys Arg Glu Ser Asp Ser Glu Arg Leu Lys Arg Thr Ser Gln Lys Val  
 245 250 255  
 Asp Leu Ala Leu Lys Gln Leu Gly His Ile Arg Glu Tyr Glu Gln Arg  
 260 265 270  
 Leu Lys Val Leu Glu Arg Glu Val Gln Gln Cys Ser Arg Val Leu Gly  
 275 280 285  
 Trp Val Ala Glu Ala Leu Ser Arg Ser Ala Leu Leu Pro Pro Gly Gly  
 290 295 300  
 Pro Pro Pro Pro Asp Leu Pro Gly Ser Lys Asp  
 305 310 315

<210> 113  
 <211> 553  
 <212> PRT  
 <213> Homo sapien

<400> 113  
 Met Val Gln Arg Leu Trp Val Ser Arg Leu Leu Arg His Arg Lys Ala  
 1 5 10 15  
 Gln Leu Leu Leu Val Asn Leu Leu Thr Phe Gly Leu Glu Val Cys Leu  
 20 25 30  
 Ala Ala Gly Ile Thr Tyr Val Pro Pro Leu Leu Leu Glu Val Gly Val  
 35 40 45  
 Glu Glu Lys Phe Met Thr Met Val Leu Gly Ile Gly Pro Val Leu Gly  
 50 55 60  
 Leu Val Cys Val Pro Leu Leu Gly Ser Ala Ser Asp His Trp Arg Gly  
 65 70 75 80  
 Arg Tyr Gly Arg Arg Arg Pro Phe Ile Trp Ala Leu Ser Leu Gly Ile  
 85 90 95  
 Leu Leu Ser Leu Phe Leu Ile Pro Arg Ala Gly Trp Leu Ala Gly Leu  
 100 105 110  
 Leu Cys Pro Asp Pro Arg Pro Leu Glu Leu Ala Leu Leu Ile Leu Gly  
 115 120 125  
 Val Gly Leu Leu Asp Phe Cys Gly Gln Val Cys Phe Thr Pro Leu Glu  
 130 135 140  
 Ala Leu Leu Ser Asp Leu Phe Arg Asp Pro Asp His Cys Arg Gln Ala  
 145 150 155 160  
 Tyr Ser Val Tyr Ala Phe Met Ile Ser Leu Gly Gly Cys Leu Gly Tyr  
 165 170 175  
 Leu Leu Pro Ala Ile Asp Trp Asp Thr Ser Ala Leu Ala Pro Tyr Leu  
 180 185 190  
 Gly Thr Gln Glu Glu Cys Leu Phe Gly Leu Leu Thr Leu Ile Phe Leu  
 195 200 205  
 Thr Cys Val Ala Ala Thr Leu Leu Val Ala Glu Glu Ala Ala Leu Gly  
 210 215 220  
 Pro Thr Glu Pro Ala Glu Gly Leu Ser Ala Pro Ser Leu Ser Pro His

[illegible]

```
<210> 114
<211> 241
<212> PRT
<213> Homo sapien
```

Met Gln Cys Phe Ser Phe Ile Lys Thr Met Met Ile Leu Phe Asn Leu															
1				5					10					15	
Leu	Ile	Phe	Leu	Cys	Gly	Ala	Ala	Leu	Leu	Ala	Val	Gly	Ile	Trp	Val
			20					25					30		
Ser	Ile	Asp	Gly	Ala	Ser	Phe	Leu	Lys	Ile	Phe	Gly	Pro	Leu	Ser	Ser
		35					40					45			
Ser	Ala	Met	Gln	Phe	Val	Asn	Val	Gly	Tyr	Phe	Leu	Ile	Ala	Ala	Gly
	50					55					60				
Val	Val	Val	Phe	Ala	Leu	Gly	Phe	Leu	Gly	Cys	Tyr	Gly	Ala	Lys	Thr
65					70					75				80	

```
<210> 115
<211> 366
<212> DNA
<213> Homo sapien
```

<400> 115						
gctctttctc	tccctctctc	tgaatttaat	tctttcaact	tgcaatttgc	aaggattaca	60
catttcaactg	tgatgtatat	tgtgttgcaa	aaaaaaaaaa	gtgtctttgt	ttaaaattac	120
rtggtttgtg	aatccatctt	gctttttccc	cattggaact	agtcattaac	ccatctctga	180
acttggtagaa	aaacatctga	agagctagtc	tatcagcctc	tgacaggtga	attggatggg	240
tctcagaacc	atttcaccca	gacagcctgt	ttctatcctg	tttaataaat	tagtttgggt	300
tctctacatg	cataacaaac	cctgctccaa	tctgtcacat	aaaagtctgt	gacttgaagt	360
ttaagtc						366

```
<210> 116
<211> 282
<212> DNA
<213> Homo sapien
```

```
<220>  
<221> misc_feature  
<222> (1)...(282)  
<223> n = A,T,C or G
```

```

<400> 116
acaaagatga accatttctct atattatagc aaaattaaaa tctaccgcta ttctaataatt 60
gagaaatgag atnaaacaca atntttataaa gtctacttag agaagatcaa gtgacctcaa 120
agactttact attttcatat ttttaagacac atgattttat ctatttttagt aaacctgggttc 180
atacgtttaa caaaggataa tgtgaacagc agagaggatt tgttggcaga aaatctatgt 240
tcaattctnq acctactana tcacagacat ttctatttct tt 282

```

```
<210> 117
<211> 305
<212> DNA
<213> Homo sapien
```

<220>  
 <221> misc\_feature  
 <222> (1)...(305)  
 <223> n = A,T,C or G

<400> 117  
 acacatgtcg cttcactgcc ttcttagatg cttctgggtca acatanagga acagggacca 60  
 tatttatcct ccttcctgaa acaattgcaa aataanacaa aatatatgaa acaattgcaa 120  
 aataaggcaa aatatatgaa acaacaggtc tcgagatatt ggaaatcagt caatgaagga 180  
 tactgatccc tgatcactgt cctaattgcag gatgtgggaa acagatgagg tcacctctgt 240  
 gactgcccc a gcttactgcc tgtagagagt ttctangctg cagttcagac agggagaaat 300  
 tgggt 305

<210> 118  
 <211> 71  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(71)  
 <223> n = A,T,C or G

<400> 118  
 accaaggtgt ntgaatctct gacgtgggga tctctgattc ccgcacaatc tgagtggaaa 60  
 aantcctggg t 71

<210> 119  
 <211> 212  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(212)  
 <223> n = A,T,C or G

<400> 119  
 actccggttg gtgtcagcag cacgtggcat tgaacatngc aatgtggagc ccaaaccaca 60  
 gaaaatgggg tgaaattggc caactttcta tnaacttatg ttggcaantt tgccaccaac 120  
 agtaagctgg cccttctaataaaaagaaaat tgaaagggtt ctcactaanc ggaattaant 180  
 aatggantca aganactccc aggcctcagc gt 212

<210> 120  
 <211> 90  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(90)  
 <223> n = A,T,C or G

<400> 120  
 actcgttgca natcaggggc cccccagagt caccgttgca ggagtccttc tggctcttgcc 60  
 ctccgcgggc gcagaacatg ctgggggtgt 90

<210> 121  
 <211> 218  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(218)  
 <223> n = A,T,C or G

<400> 121  
 tgtanogtga anacgacaga nagggttgtc aaaaatggag aanccttgaa gtcattttga 60  
 gaataagatt tgctaaaaga ttgggggcta aaacatgggtt attgggagac atttctgaag 120  
 atatncangt aaattangga atgaattcat gggtcttttg ggaattcctt tacgatngcc 180  
 agcatanact tcatgtgggg atancageta ccttgta 218

<210> 122  
 <211> 171  
 <212> DNA  
 <213> Homo sapien

<400> 122  
 taggggtgta tgcaactgta aggacaaaaa ttgagactca actggcttaa ccaataaagg 60  
 catttgtag ctcatggaac aggaagtcgg atgggtggggc atcttcagtg ctgcatgagt 120  
 caccaccccg ggggggtcat ctgtgccaca ggccctgtt gacagtgcgg t 171

<210> 123  
 <211> 76  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(76)  
 <223> n = A,T,C or G

<400> 123  
 tgtagcgtga agacnacaga atggtgtgtg ctgtgctatc caggaacaca tttattatca 60  
 ttatcaanta ttgtgt 76

<210> 124  
 <211> 131  
 <212> DNA  
 <213> Homo sapien

<400> 124  
 acctttcccc aaggccaatg tctgtgtgta taactggcgg gctgcaggac agctgcaatt 60  
 caatgtgctg ggtcatatgg aggggaggag actctaaaat agccaatttt attctcttgg 120  
 ttaagatttg t 131

<210> 125  
 <211> 432  
 <212> DNA  
 <213> Homo sapien

<400> 125  
 acctttatcta ctggctatga aatagatggg ggaaaattgc gttaccaact ataccactgg 60  
 ctgaaaaaag aggtgatagc tcttcagagg acttgtgact ttgtctcaga tgctgaagaa 120

```

ctacagtctg catttggcag aaatgaagat gaatttggat taaatgagga tgcgaagat 180
ttgcctcacc aaacaaaagt gaaacaactg agagaaaatt ttcaggaaaa aagacagtgg 240
ctcttgaagt atcagtcact ttgagaatg tttcttagtt actgcatact tcatggatcc 300
catggtgggg gtcttgcacg tgtaagaatg gaattgattt tgcttttgca agaattctcag 360
caggaaacat cagaaccact attttctagc cctctgtcag agcaaaccctc agtgcctctc 420
ctctttgctt gt 432

```

```

<210> 126
<211> 112
<212> DNA
<213> Homo sapien

```

```

<400> 126
acacaacttg aatagtaaaa tagaaactga gctgaaattt ctaattcact ttctaaccat 60
agtaagaatg atatttcccc ccagggatca ccaaatattt ataaaaattt gt 112

```

```

<210> 127
<211> 54
<212> DNA
<213> Homo sapien

```

```

<400> 127
accacgaaac cacaacaag atggaagcat caatccactt gccaaagcaca gcag 54

```

```

<210> 128
<211> 323
<212> DNA
<213> Homo sapien

```

```

<400> 128
acctcattag taattgtttt gttgtttcat ttttttctaa tgtctcccct ctaccagctc 60
acctgagata acagaatgaa aatggaagga cagccagatt tctcctttgc tctctgtcga 120
ttctctctga agtctaggtt acccattttg gggacccatt ataggcaata aacacagttc 180
ccaaagcatt tggacagttt cttgtttgtgt tttagaatgg ttttcctttt tcttagcctt 240
ttcctgcaaa aggctcactc agtcccttgc ttgctcagtg gactgggctc cccagggcct 300
aggctgcctt cttttccatg tcc 323

```

```

<210> 129
<211> 192
<212> DNA
<213> Homo sapien

```

```

<220>
<221> misc_feature
<222> (1)...(192)
<223> n = A,T,C or G

```

```

<400> 129
acatacatgt gtgtatattt ttaaataatca cttttgtatc actctgactt tttagcatac 60
tgaaaacaca ctaacataat tntgtgaac catgatcaga tacaacccaa atcattcatc 120
tagcacattc atctgtgata naaagatagg tgagtttcat ttccttcacg ttggccaatg 180
gataaacaaa gt 192

```

```

<210> 130
<211> 362
<212> DNA
<213> Homo sapien

```

<220>  
 <221> misc\_feature  
 <222> (1)...(362)  
 <223> n = A,T,C or G

<400> 130  
 cccttttttta tggaatgagt agactgtatg tttgaanatt tanccacaac ctcttttgaca 60  
 catatgacg caacaaaaag gtgctgttta gtccatgggt tcagtttatg cccctgacaa 120  
 gtttccattg tggtttgcg atcttctggc taatcgtgggt atcctccatg ttattagtaa 180  
 ttctgtattc cattttgtta acgcttggt gatgtaacct gctangaggc taactttata 240  
 ctattttaaa agctcttatt ttgtggtcat taaaatggca atttatgtgc agcactttat 300  
 tgcagcagga agcaogtgtg ggttggttg aaagctctt gctaacttta aaaagtaatg 360  
 gg

<210> 131  
 <211> 332  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(332)  
 <223> n = A,T,C or G

<400> 131  
 ctttttgaaa gatcgtgtcc actcctgtgg acatcttgtt ttaatggagt ttcccatgca 60  
 gtangactgg tatggttgca gctgtccaga taaaaacatt tgaagagctc caaaatgaga 120  
 gttctccag gttcgcctg ctgctccaag tctcagcagc agcctctttt aggaggcatc 180  
 ttctgaacta gattaaggca gcttgtaa atctgatgtgat ttgggtttatt atccaactaa 240  
 ctcccatctg ttatcactgg agaaagccca gactcccan gacnggtacg gattgtgggc 300  
 atanaaggat tgggtgaagc tggcgttggt gt 332

<210> 132  
 <211> 322  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(322)  
 <223> n = A,T,C or G

<400> 132  
 acttttgcca ttttgtatat ataaacaatc ttgggacatt ctcttgaaaa ctaggtgtcc 60  
 agtggctaag agaactcgat ttcaagcaat tctgaaagga aaaccagcat gacacagaat 120  
 ctcaaattcc caaacagggg ctctgtggga aaaatgaggg aggacctttg tatctcgggt 180  
 ttttagcaagt taaaatgaan atgacaggaa aggccttatt atcaacaaag agaagagttg 240  
 ggatgcttct aaaaaaaact ttggtagaga aaataggaat gctnaatcct agggaagcct 300  
 gtaacaatct acaattgggt ca 322

<210> 133  
 <211> 278  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(278)

<223> n = A,T,C or G

<400> 133

acaagccttc	acaagttttaa	ctaaattggg	attaatcttt	ctgtanttat	ctgcataatt	60
cttgtttttc	tttccatctg	gctcctgggt	tgacaatttg	tggaacaac	tctattgcta	120
ctatttaaaa	aaaatcacia	atctttccct	ttaagctatg	ttnaattcaa	actattcctg	180
ctattcctgt	tttgtcaaag	aaattatatt	tttcaaaaata	tgtntatttg	tttgatgggt	240
cccacgaaac	actaataaaa	accacagaga	ccagcctg			278

<210> 134

<211> 121

<212> DNA

<213> Homo sapien

<220>

<221> misc\_feature

<222> (1)...(121)

<223> n = A,T,C or G

<400> 134

gtttanaaaa	cttgttttagc	tccatagagg	aaagaatggt	aaactttgta	ttttaaaaca	60
tgattctctg	agggttaaact	tggttttcaa	atgttatatt	tacttgatt	ttgcttttg	120
t						121

<210> 135

<211> 350

<212> DNA

<213> Homo sapien

<220>

<221> misc\_feature

<222> (1)...(350)

<223> n = A,T,C or G

<400> 135

acttanaacc	atgcctagca	catcagaatc	cctcaaagaa	catcagtata	atcctatacc	60
atancaagt	gtgactggtt	aagcgtgcga	caaaggtcag	ctggcacatt	acttggtgtc	120
aaacttgata	cttttggtct	aagttagaac	tagtatacag	tnccctagga	tggtactcca	180
gggtgcccc	caactcctgc	agccgtcct	ctgtgccagn	ccctgnaagg	aactttcgt	240
ccacctcaat	caagccctgg	gccatgctac	ctgcaattgg	ctgaacaaac	gtttgctgag	300
ttcccaagga	tgcaaagcct	ggtgctcaac	tcctggggcg	tcaactcagt		350

<210> 136

<211> 399

<212> DNA

<213> Homo sapien

<220>

<221> misc\_feature

<222> (1)...(399)

<223> n = A,T,C or G

<400> 136

tgtaccgtga	agacgacaga	agttgcatgg	cagggacagg	gcagggccga	ggccagggtt	60
gctgtgattg	tatccgaata	ntcctcgtga	gaaaagataa	tgagatgacg	tgagcagcct	120
gcagacttgt	gtctgccttc	aanaagccag	acaggaaggc	cctgcctgcc	ttggctctga	180
cctggcggcc	agccagccag	ccacagggtg	gcttcttcct	tttgtggtga	caacnccaag	240
aaaactgcag	aggcccagg	tcagggtgna	gtgggtangt	gaccataaaa	caccagggtc	300



tccatgggaac cccgggcaaaag gccatcccca cctacagcca gcctgcccac tggcgtgatg 360  
 gctgcagang gatgaagcag ccagntgttc tctcttggt 399

<210> 137  
 <211> 165  
 <212> DNA  
 <213> Homo sapien  
 <220>  
 <221> misc\_feature  
 <222> (1)...(165)  
 <223> n = A,T,C or G

<400> 137  
 actggtgttg tngggg; tga tctgtggtgt anaagttgan gtgacttcan gatggtgtgt 60  
 ggagdaaqtg tctgaagta gggatgtaga ngttttggcc gtgctaaatg agcttcggga 120  
 ttgctgtgtc ccactggttg tcaactgtcat tgggtggggt cctgt 165

<210> 136  
 <211> 338  
 <212> DNA  
 <213> Homo sapien  
 <220>  
 <221> misc\_feature  
 <222> (1)...(338)  
 <223> n = A,T,C or G

<400> 138  
 actcactgga atgccacatt cacaacagaa tcagaggtct gtgaaaacat taatggctcc 60  
 ttaacttctc cagtaagaat cagggaacttg aaatggaaac gttaacagcc acatgoccaa 120  
 tgetgggcag tctcccatgc cttccacagt gaaagggctt gagaaaaatc acatccaatg 180  
 tcatgtgttt ccagccacac caaaaggtgc ttgggggtgga gggctggggg catananggt 240  
 cangcctcag gaagcctcaa gttccattca gctttgccac tgtacattcc ccatntttaa 300  
 aaaaactgat gccttttttt tttttttttg taaaattc 338

<210> 139  
 <211> 382  
 <212> DNA  
 <213> Homo sapien

<400> 139  
 gggaatcttg gtttttggca tctggtttgc ctatagccga ggccactttg acagaacaaa 60  
 gaaagggact tgcagtaaga aggtgattta cagccagcct agtccccgaa gtgaaggaga 120  
 attcaaacag acctcgtcat tctgtgtgtg agcctggctg gctcacgcc tatcatctgc 180  
 atttgcctta ctcaggtgct accggactct ggccttgat gtctgtagt ttacaggatg 240  
 ccttattttgt cttctacacc ccacagggcc cctacttct tgggatgtgt ttttaataat 300  
 gtcagctatg tgcctcatcc tcttcatgc cctccctccc ttctctacca ctgctgagtg 360  
 gcttgaact tgtttaaagt gt 382

<210> 140  
 <211> 200  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(200)

<223> n = A,T,C or G

<400> 140

acccaaanctt	ctttctgttg	tgttngattt	tactataggg	gtttngcttn	ttctaaanat	60
acttttcatt	taacancctt	tgtaagtgt	caggctgcac	tttgcctcat	anaattattg	120
ttttcacatt	tcaacttgta	tgtgtttgtc	tcttanagca	ttggtgaaat	cacatatttt	180
atattcagca	taaaggagaa					200

<210> 141

<211> 335

<212> DNA

<213> Homo sapien

<220>

<221> misc\_feature

<222> (1)...(335)

<223> n = A,T,C or G

<400> 141

actttatttt	caaaacactc	atatgttgca	aaaaacacat	agaaaaataa	agtttggtgg	60
gggtgctgac	taaacttcaa	gtcacagact	tttatgtgac	agattggagc	agggtttggt	120
atgcatgtag	agaacccaaa	ctaattttatt	aaacaggata	gaaacaggct	gtctgggtga	180
aatggttctg	agaaccatcc	aattcacctg	tcagatgctg	atanactagc	tcttcagatg	240
tttttctacc	agttcagaga	tnggttaatg	actanttcca	atgggggaaa	agcaagatgg	300
attcacaac	caagtaattt	taaacaaaga	cactt			335

<210> 142

<211> 459

<212> DNA

<213> Homo sapien

<220>

<221> misc\_feature

<222> (1)...(459)

<223> n = A,T,C or G

<400> 142

accaggttaa	tattgccaca	tatatccttt	ccaattgcgg	gctaaacaga	cgtgtattta	60
gggttggtta	aagacaaccc	agcttaatat	caagagaaat	tgtgaccttt	catggagtat	120
ctgatggaga	aaacactgag	ttttgacaaa	tcttatttta	ttcagatagc	agtctgatca	180
cacatgggtcc	aacaacactc	aaataataaa	tcaaatatna	tcagatgtta	aagattggtc	240
ttcaaacatc	atagccaatg	atgccccgct	tgccctataat	ctctccgaca	taaaaccaca	300
tcaacacctc	agtgggccacc	aaaccattca	gcacagcttc	cttaactgtg	agctggttga	360
agctaccagt	ctgagcaeta	ttgactatnt	ttttcangct	ctgaatagct	ctagggatct	420
cagcangggg	gggaggaacc	agctcaacct	tggcgtant			459

<210> 143

<211> 140

<212> DNA

<213> Homo sapien

<400> 143

acatttcctt	ccaccaagtc	aggactcctg	gcttctgtgg	gagttcttat	cacctgaggg	60
aaatccaaac	agtctctcct	agaaaggaat	agtgccacca	accccaacca	tctccctgag	120
accatccgac	ttccctgtgt					140

<210> 144

<211> 164

```

<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(164)
<223> n = A,T,C or G

<400> 144
acttcagtaa caacatacaa taacaacatt aagtgtatat tgccatcttt gtcattttct      60
atctatacca ctctcccttc tgaaaacaan aatcactanc caatcactta tacaaaatttg      120
aggcaattaa tccatatttg ttttcaataa ggaaaaaaag atgt                        164

<210> 145
<211> 303
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(303)
<223> n = A,T,C or G

<400> 145
acgtagacca tccaactttg tatttgtaat ggcaaacatc cagnagcaat tcctaaacaa      60
actggagggt atttataccc aattatccca ttcattaaca tgccctcctc ctcaggctat      120
gcaggacagc tatcataagt cggcccaggc atccagatac taccatttgt ataaacttca      180
gtaggggagt ccatccaagt gacaggtcta atcaaaggag gaaatggaac ataagcccag      240
tagtaaaatn ttgcttagct gaaacagcca caaaagactt accgccgtgg tgattaccat      300
caa                                                                303

<210> 146
<211> 327
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(327)
<223> n = A,T,C or G

<400> 146
actgcagctc aattagaagt ggtctctgac tttcatcanc ttctccctgg gctccatgac      60
actggcctgg agtgactcat tgcctctggt gggtgagaga gctcctttgc caacaggcct      120
ccaagtcagg gctgggattt gtttcctttc cacattctag caacaatatg ctggccactt      180
cctgaacagg gagggtggga ggagccagca tggaacaagc tgccactttc taaagtagcc      240
agacttgccc ctgggcctgt cacacctact gatgaccttc tgtgcctgca ggatggaatg      300
taggggtgag ctgtgtgact ctatggt                                     327

<210> 147
<211> 173
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(173)
<223> n = A,T,C or G

```

<400> 147  
 acattgtttt tttagataa agcattgana gagctctcct taacgtgaca caatggaagg 60  
 actggaacac ataccacat ctttgttctg agggataatt ttctgataaa gtcttgctgt 120  
 atattcaagc acatatgtta tatattatc agttccatgt ttatagccta gtt 173

<210> 148  
 <211> 477  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(477)  
 <223> n = A,T,C or G

<400> 148  
 acaaccactt tatctcatcg aatttttaac ccaaactcac tcaactgtgcc tttctatcct 60  
 atgggatata ttatttgatg ctccatttca tcacacatat atgaataata cactcatact 120  
 gccctactac ctgctgcaat aatcacattc ccttcctgtc ctgaccctga agccattggg 180  
 gtggctctag tggccatcag tccangcctg cacccttgagc ccttgagctc cattgctcac 240  
 nccancccac ctccaccgacc ccctcctctt acacagctac ctcttgctc tctaacccca 300  
 tagattatnt ccaaattcag tcaattaagt tactattaac actctaccgg acatgtccag 360  
 caccactggt aagccttctc cagccaacac acacacacac acacncacac acacacatat 420  
 ccaggcacag gctacctcat cttcacaatc acccctttaa ttaccatgct atggtgg 477

<210> 149  
 <211> 207  
 <212> DNA  
 <213> Homo sapien

<400> 149  
 acagttgtat tataatatca agaaataaac ttgcaatgag agcatttaag agggaagaac 60  
 taacgtatnt tagagagcca aggaagggtt ctgtggggag tgggatgtaa ggtggggcct 120  
 gatgataaat aagagtcagc caggtaagtg ggtggtgtgg tatgggcaca gtgaagaaca 180  
 tttcaggcag agggaacagc agtgaaa 207

<210> 150  
 <211> 111  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(111)  
 <223> n = A,T,C or G

<400> 150  
 accttgattt cattgctgct ctgatggaaa cccaactatc taatttagct aaaacatggg 60  
 cacttaaagt tggtcagtgt ttggacttgt taactantgg catctttggg t 111

<210> 151  
 <211> 196  
 <212> DNA  
 <213> Homo sapien

<400> 151  
 agcgcggcag gtcatttga acattccaga tacctatcat tactcgatgc tgttgataac 60

```

aggaagatgg ctttgaactc agggtcacca ccagctattg gaccttacta tgaaaaccat 120
ggataccaac cggaaaaccc ctatcccgca cagcccactg tggccccac tgtctacgag 180
gtatctcgg ctcagt 196

```

```

<210> 152
<211> 132
<212> DNA
<213> Homo sapien

```

```

<400> 152
aaagaaattt cacatgtaag aaggagaaaa ttctaaatg taggagaaag ataacagAAC 60
cttccatctt tcatctagt gtggaaacct gatgctttat gttgacagga atagaaccag 120
gaggagattt gt 132

```

```

<210> 153
<211> 285
<212> DNA
<213> Homo sapien

```

```

<220>
<221> misc_feature
<222> (1)...(285)
<223> n = A,T,C or G

```

```

<400> 153
acaanaccca nganaggcca ctggccgtgg tgtcatggcc tccaaacatg aaagtgtcag 60
cttctgctct tatgtctctc tctgacaact ctttaccatt tttatctctg ctcagcagga 120
gcacatcaat aaagtccaaa gtcttgact tggccttggc ttggaggaag tcatcaacac 180
cctggctagt gagggtgagg cgcgcctcct ggatgacggc atctgtgaag tctgtcacca 240
gtctgcaggc cctgtggaag cgcgcctcac acggagtnag gaatt 285

```

```

<210> 154
<211> 333
<212> DNA
<213> Homo sapien

```

```

<400> 154
accacagtc tgttggggcca gggcttcctg accctttctg tgaaaagcca tattatcacc 60
accccaaat tttctttaa tatctttaac tgaaggggtc agcctcttga ctgcaaagac 120
cctaagcgg ttacacagct aactccact ggccctgatt tgtgaaattg ctgtgcctg 180
attggcacag gattcgaagg tttcagctc cctcctcgg tggaacgaga ctctgattg 240
agtttcaca attctggggc cacctcgtca ttgtcctct gaaataaaat cgggagaatg 300
gtcaggcctg tctcatccat atggatcttc cgg 333

```

```

<210> 155
<211> 308
<212> DNA
<213> Homo sapien

```

```

<220>
<221> misc_feature
<222> (1)...(308)
<223> n = A,T,C or G

```

```

<400> 155
atcaggaaata ataaaaccca catcacagt ttgtgtcaaa gatcatcagg gcatggatgg 60
aaagtgcctt tgggaactgt aaagtgccta acacatgac gatgattttt gttataatat 120
ttgattcag gtgcatacaa actctcctgc ctgctcctcc tgggccccag cccagcccc 180

```

atcacagctc actgctctgt tcatccaggc ccagcatgta gtggctgatt cttcttggt	240
gcttttagcc tccanaagtt tctctgaagc caaccaaacc tctangtgta aggcattgctg	300
gccctgg	308

<210> 156  
 <211> 295  
 <212> DNA  
 <213> Homo sapien

<400> 156	
accttgctcg gtgcttgga catattagga actcaaaata tgagatgata acagtgccta	60
ttattgatta ctgagagaac tgtagacat ttagttgaag attttctaca caggaactga	120
gaataggaga ttatgtttgg cctcatatt ctctcctatc ctcttgctt cattctatgt	180
ctaatatatt ctcaatcaaa taaggtagc ataatcagga aatcgaccaa ataccaatat	240
aaaaccagat gtctatcctt aagattttca aatagaaaac aaattaacag actat	295

<210> 157  
 <211> 126  
 <212> DNA  
 <213> Homo sapien

<400> 157	
acaagtttaa atagtgtgt cactgtgcat gtgctgaaat gtgaaatcca ccacatttct	60
gaagagcaaa acaaattctg tcatgtaatc tctatcttgg gtcgtgggta tatctgtccc	120
cttagt	126

<210> 158  
 <211> 442  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(442)  
 <223> n = A,T,C or G

<400> 158	
accactgggt cttggaaaca cccatcotta atacgatgat ttttctgtcg tgtgaaaatg	60
aanccagcag gctgccccta gtcagtcctt ccttcagag aaaaagagat ttgagaaagt	120
gcctgggtaa ttcaaccatta atttcctccc ccaaactctc tgagtcttcc cttaatatgt	180
ctggtggttc tgaccaaagc aggtcatggt ttgttgagca tttgggatcc cagtgaagta	240
natgtttgta gccttgcata cttagccctt cccacgcaca aacggagtgg cagagtgggtg	300
ccaaccctgt tttcccagtc cacttagaca gattcacagt gcggaattct ggaagctgga	360
nacagacggg ctctttgcag agccgggact ctgagangga catgagggcc tctgcctctg	420
gtttcattct ctgatgtcct gt	442

<210> 159  
 <211> 498  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(498)  
 <223> n = A,T,C or G

<400> 159	
acttccaggt aacgttgttg tttccgttga gcctgaactg atgggtgacg ttgtaggttc	60

```

tccaacaaga actgaggttg cagagcgggt aggggaagagt gctgttccag ttgcacctgg 120
gctgctgttg actgttgttg attcctcact acggcccaag gttgtggaac tggcanaaag 180
gtatattgtt gganttgagc tcgggcgggt gtggtaggtt gtgggcctct caacaggggc 240
gtgtgtgttg ccgggangtg aangtggttg gtcacttgag cttggccagc tctggaaaag 300
antanattct tctgaaggc cagcgttgt ggagctggca ngggtcantg ttgtgtgtaa 360
cgaaccagtg ctgctgtggg tgggtgtana tctccacaa agcctgaagt tatggtgtcn 420
tcaggtaana atgtggttct agtgtccctg ggcnctgtg gaaggttgta nattgtcacc 480
aggggaataa gctgtggt 498

```

```

<210> 160
<211> 380
<212> DNA
<213> Homo sapien

```

```

<220>
<221> misc_feature
<222> (1)...(380)
<223> n = A,T,C or G

```

```

<400> 160
acctgcatcc agcttccctg ccaaactcac aaggagacat caacctctag acagggaaac 60
agcttcagga tacttccagg agacagagcc accagcagca aaacaaatat tcccatgcct 120
ggagcatggc atagaggaag ctganaaatg tgggtctgga ggaagccatt tgagtctggc 180
cactagacat ctcacagcc acttgtgtga agagatgcc catgaccoca gatgcctctc 240
ccaccettac ctccatctca cacacttgag ctttccactc tgtataattc taacatcctg 300
gagaaaaatg gcagtttgac cgaacctgtt cacaacggta gaggetgatt tctaacgaaa 360
cttgtagaat gaagcctgga 380

```

```

<210> 161
<211> 114
<212> DNA
<213> Homo sapien

```

```

<400> 161
actccacatc cctctgagc aggcggttgt cgttcaaggt gtatttggcc ttgcctgtca 60
cactgtccac tggcccctta tcacttggg gcttaatccc tcgaaagagc atgt 114

```

```

<210> 162
<211> 177
<212> DNA
<213> Homo sapien

```

```

<400> 162
actttctgaa tcgaatcaaa tgatacttag tgtagtttta atatcctcat atatatcaaa 60
atttactac tctgataatt ttgtaaaacca ggtaaccaga acatccagtc atacagcttt 120
tggatgata taacttggca ataaccagc ctggtgatac ataaaactac tcactgt 177

```

```

<210> 163
<211> 137
<212> DNA
<213> Homo sapien

```

```

<220>
<221> misc_feature
<222> (1)...(137)
<223> n = A,T,C or G

```

```

<400> 163

```

```

catttataca gacagggcgtg aagacattca cgacaaaaaac gcgaaattct atcccgtgac      60
canagaaggc agctacggct actcctacat cctggcggtgg gtggccttcg cctgcacctt      120
catcagcggc atgatgt                                     137

```

```

<210> 164
<211> 469
<212> DNA
<213> Homo sapien

```

```

<220>
<221> misc_feature
<222> (1)...(469)
<223> n = A,T,C or G

```

```

<400> 164
cttatcacia tgaatgttct cctgggcagc gttgtgatct ttgccacctt cgtgacttta      60
tgcaatgcat catgctatct catacctaata gagggagttc caggagattc aaccaggaaa      120
tgcatggatc tcaaaggaaa caaacaccca ataaactcgg agtggcagac tgacaactgt      180
gagacatgca cttgtctacga aacagaaatt tcatgttgca cccttgtttc tacacctgtg      240
ggttatgaca aagacaactg ccaaagaatc ttcaagaagg aggactgcaa gtatatcgtg      300
gtggagaaga aggacccaaa aaagacctgt tctgtcagtg aatggataat ctaatgtgct      360
tctagtaggc acagggtctc caggccaggc ctcatctctc tctggcctct aatagtcaat      420
gattgtgtag ccatgcctat cagtaaaaag atntttgagc aaacacttt                    469

```

```

<210> 165
<211> 195
<212> DNA
<213> Homo sapien

```

```

<220>
<221> misc_feature
<222> (1)...(195)
<223> n = A,T,C or G

```

```

<400> 165
acagtttttt atanatctcg acattgccgg cacttggtgtt cagtttcata aagctgggtgg      60
atccgctgtc atccactatt ccttggttag agtaaaaaatt attcttatag cccatgtccc      120
tgcaggccgc ccgcccgtag ttctcgttcc agtcgtcttg gcacacaggg tgccaggact      180
tcctctgaga tgagt                                     195

```

```

<210> 166
<211> 383
<212> DNA
<213> Homo sapien

```

```

<220>
<221> misc_feature
<222> (1)...(383)
<223> n = A,T,C or G

```

```

<400> 166
acatcttagt agtgtggcac atcagggggc catcagggtc acagtcactc atagcctcgc      60
cgaggctgga gtccacacca ccggtgtagg tgtgtcaaat cttgggcttg gcgcccacct      120
ttggagaagg gatagtctgc acacacatgt ccacaaagcc tgtgaactcg ccaaagaatt      180
tttgagacc agcctgagca aggggcggat gtccagcttc agctcctctc tcgtcagggtg      240
gatgccaaac tcgtctangg tccgtgggaa gctgggtgtc acntcaccta caacctgggc      300
gangatctta taaagaggct ccnagataaa ctccacgaaa cttctctggg agctgctagt      360
nggggccttt ttggtgaact ttc                                     383

```



<210> 167  
 <211> 247  
 <212> DNA  
 <213> Homo sapien  
  
 <220>  
 <221> misc\_feature  
 <222> (1)...(247)  
 <223> n = A,T,C or G

<400> 167  
 acagagccag accctggcca taaatgaanc agagattaag actaaacccc aagtcganat 60  
 tggagcagaa actggagcaa gaagtggggc tggggctgaa gtagagacca aggccactgc 120  
 tatandcata cacagagcca actctcaggc caaggcnatg gttggggcag anccagagac 180  
 tcaatctgan tccaaagtgg tggctggaac actggtcatg acanaggcag tgactctgac 240  
 tgangtc 247

<210> 168  
 <211> 273  
 <212> DNA  
 <213> Homo sapien  
  
 <220>  
 <221> misc\_feature  
 <222> (1)...(273)  
 <223> n = A,T,C or G

<400> 168  
 acttctaagt tttctagaag tggaaggatt gtantcatcc tgaaaatggg tttacttcaa 60  
 aatccctcan ccttgttctt cactactgtc tatactgana gtgtcatgtt tccacaaagg 120  
 gctgacacct gagcctgnat tttcactcat ccttgagaag ccctttccag taggggtggc 180  
 aattcccaac ttcttgcca caagcttccc aggetttctc ccctggaaaa ctccagcttg 240  
 agtccagat acactcatgg gctgccctgg gca 273

<210> 169  
 <211> 431  
 <212> DNA  
 <213> Homo sapien  
  
 <220>  
 <221> misc\_feature  
 <222> (1)...(431)  
 <223> n = A,T,C or G

<400> 169  
 acagccttgg cttccccaaa ctccacagtc tcagtgcaga aagatcatct tccagcagtc 60  
 agctcagacc aggttcaaag gatgtgacat caacagtttc tggtttcaga acaggttcta 120  
 ctactgtcaa atgacccccc atacttctc aaaggctgtg gtaagttttg cacaggtgag 180  
 ggcagcagaa aggggttant tactgatgga caccatcttc tctgtatact ccacactgac 240  
 ctltgccatgg gcaaaggccc ctaccacaaa aacaatagga tcaactgctgg gcaccagctc 300  
 acgcacatca ctgacaaccg ggatggaaaa agaantgcc aatttcatac atccaactgg 360  
 aaagtgatct gatactggat tcttaattac cttcaaaagc ttctgggggc catcagctgc 420  
 tgaacactg a 431

<210> 170  
 <211> 266  
 <212> DNA

<213> Homo sapien

<220>

<221> misc\_feature

<222> (1)...(266)

<223> n = A,T,C or G

<400> 170

acctgtgggc	tgggctgtta	tgccgtgtgcc	ggctgtctgaa	agggagttca	gaggtggagc	60
tcaaggagct	ctgcaggcat	tttgccaanc	ctctccanag	canagggagc	aacctacact	120
ccccgctaga	aagacaccag	attggagtcc	tgggaggggg	agttgggggtg	ggcatttgat	180
gtatacttgt	cacctgaatg	aangagccag	agaggaanga	gacgaanatg	anattggcct	240
tcaaagctag	gggtctggca	ggtgga				266

<210> 171

<211> 1248

<212> DNA

<213> Homo sapien

<220>

<221> misc\_feature

<222> (1)...(1248)

<223> n = A,T,C or G

<400> 171

ggcagccaaa	tcataaacgg	cgaggactgc	agcccgcaact	cgagccctg	gcaggcggea	60
ctggtcatgg	aaaacgaatt	gttctgctcg	ggcgtcctgg	tgcatccgca	gtgggtgctg	120
tcagccgcac	actgtttcca	gaagtgagtg	cagagctcct	acaccatcgg	gctgggcctg	180
cacagtcttg	aggccgacca	agagccagg	agccagatgg	tggaggccag	cctctccgta	240
cggcaccag	agtacaacag	acccttgctc	gctaaccgacc	tcattgctcat	caagttggac	300
gaatccgtgt	ccgagtctga	caccatccgg	agcatcagca	ttgcttcgca	gtgccctacc	360
gcggggaact	cttgccctcg	ttctggctgg	ggtctgctgg	cgaacggcag	aatgcctacc	420
gtgctgcagt	gcgtgaacgt	gtcgggtggtg	tctgaggagg	tctgcagtaa	gctctatgac	480
ccgctgtacc	acccagcag	gttctgcgcc	ggcggagggg	aagaccagaa	ggactcctgc	540
aacgggtgact	ctggggggcc	cctgatctgc	aacgggtact	tgacgggcct	tgtgtctttc	600
ggaaaagccc	cgtgtggcca	agttggcgtg	ccaggtgtct	acaccaacct	ctgcaaattc	660
actgagtggg	tagagaaaac	cgtccaggcc	attcaggaat	atctgttccc	agccctcct	720
attgaccccc	aaatacatcc	tgcggaagga				780
ccctcaggcc	caggagtcca	ggccccagc	ccctcctccc	tcaaaccaag	ggtacagatc	840
cccagcccct	cctccctcag	acccaggagt	ccagaccccc	cagccctccc	tccctcagac	900
ccaggagtcc	agccctcct	ccctcagacc	caggagtcca	gacccccag	cccctcctcc	960
ctcagaccca	ggggtccagg	cccccaaccc	ctcctccctc	agactcagag	gtccaagccc	1020
ccaaccntc	attccccaga	cccagagggtc	cagggtcccag	ccctcctccc	ctcagaccca	1080
gcggtccaat	gccacctaga	ctntccctgt	acacagtgcc	cccttggtggc	acgttgaccc	1140
aaccttacca	gttggttttt	catttttngt	ccctttcccc	tagatccaga	aataaagttt	1200
aagagaagng	caaaaaaaaa	aaaaaaaaaa	aaaaaaaaaa	aaaaaaaa		1248

<210> 172

<211> 159

<212> PRT

<213> Homo sapien

<220>

<221> VARIANT

<222> (1)...(159)

<223> Xaa = Any Amino Acid

<400> 172

```

Met Val Glu Ala Ser Leu Ser Val Arg His Pro Glu Tyr Asn Arg Pro
 1           5           10           15
Leu Leu Ala Asn Asp Leu Met Leu Ile Lys Leu Asp Glu Ser Val Ser
      20           25           30
Glu Ser Asp Thr Ile Arg Ser Ile Ser Ile Ala Ser Gln Cys Pro Thr
      35           40           45
Ala Gly Asn Ser Cys Leu Val Ser Gly Trp Gly Leu Leu Ala Asn Gly
      50           55           60
Arg Met Pro Thr Val Leu Gln Cys Val Asn Val Ser Val Val Ser Glu
      65           70           75           80
Glu Val Cys Ser Lys Leu Tyr Asp Pro Leu Tyr His Pro Ser Met Phe
      85           90           95
Cys Ala Gly Gly Gly Gln Xaa Gln Xaa Asp Ser Cys Asn Gly Asp Ser
      100           105           110
Gly Gly Pro Leu Ile Cys Asn Gly Tyr Leu Gln Gly Leu Val Ser Phe
      115           120           125
Gly Lys Ala Pro Cys Gly Gln Val Gly Val Pro Gly Val Tyr Thr Asn
      130           135           140
Leu Cys Lys Phe Thr Glu Trp Ile Glu Lys Thr Val Gln Ala Ser
      145           150           155

```

```

<210> 173
<211> 1265
<212> DNA
<213> Homo sapien

```

```

<220>
<221> misc_feature
<222> (1)...(1265)
<223> n = A,T,C or G

```

```

<400> 173
ggcagcccgcc actgcagccc ctggcagggc gcactggtca tggaaaacga attgtttctgc      60
tcggggcgctcc tgggtgcatcc gcagtggggtg ctgtcagccc cacactgttt ccagaactcc      120
tacaccatcg ggctgggccc gcacagtctt gaggccgacc aagagccagg gagccagatg      180
gtggaggcca gcctctccgt acggcaccca gactacaaca gacccttgct cgctaaccgac      240
ctcatgctca tcaagttgga cgaatccgtg tccgagtctg acaccatccg gagcatcagc      300
attgtttcgc agtgccctac cgcggggaac tcttgccctg tttctggctg ggggtctgctg      360
gcgaacgggtg agctcacggg tgtgtgtctg ccctcttcaa ggaggtcctc tgcccagtcg      420
cgggggctga cccagagctc tgcgtcccag gcagaatgcc taccgtgctg cagtgcgtga      480
acgtgtcggt ggtgtctgag gaggtctgca gtaagctcta tgaccgcgtg taccacccca      540
gcattgtctg cgcgggggga gggcaagacc agaaggactc ctgcaacggg gactctgggg      600
ggccctgat ctgcaacggg tacttgagg gccttggtc tttcggaaaa gcccctgtg      660
gccaagttgg cgtgccaggt gtctacacca acctctgcaa attcactgag tggatagaga      720
aaaccgtcca ggccagttaa ctctggggac tgggaaccca tgaaattgac ccccaaatac      780
atctcgga aggaattcag gaatatctgt tcccagcccc tctcctccta ggcccaggag      840
tccaggcccc cagccctcc tccctcaaac caagggtaca gatccccagc cctcctccc      900
tcagaccag gagtcagac ccccagccc ctctcctc agaccagga gtccagcccc      960
tctcctntca gaccaggag tccagacccc ccagccctc ctccctcaga cccaggggtt      1020
gagggcccca accctcctc cttcagagtc agagggtccaa gcccccaacc cctcggtccc      1080
cagaccaga ggttnaggtc ccagccctc ttcctcaga cccagnggtc caatgccacc      1140
tagattttcc ctgnacacag tgccccctg tggngnggtg acccaacctt accagttggg      1200
tttcatattt tngtcccttt ccctagatc cagaaataaa gtttaagaga ngngcaaaaa      1260
aaaaa

```

```

<210> 174
<211> 1459
<212> DNA

```

<213> Homo sapien

<220>

<221> misc\_feature

<222> (1)...(1459)

<223> n = A,T,C or G

<400> 174

ggtcagccgc	acactgtttc	cagaagtgc	tgcagagctc	ctacaccatc	gggctgggccc	60
tgcacagtct	tgaggccgac	caagagccag	ggagccagat	gggtggaggcc	agcctctccg	120
tacggcacc	agagtacaac	agacccttgc	tcgctaacga	cctcatgctc	atcaagttgg	180
acgaatccgt	gtccgagtct	gacaccatcc	ggagcatcag	cattgcttcg	cagtgcctta	240
ccgcggggaa	ctcttgccct	gtttctggct	ggggtctgct	ggcgaacggg	gagctcacgg	300
gtgtgtgtct	gccctcttca	aggaggtcct	ctgcccagtc	gcgggggctg	accagagct	360
ctgcgtccca	ggcagaatgc	ctaccgtgct	gcagtgcgtg	aacgtgtcgg	tgggtgtctga	420
ngagggtctgc	antaagctct	atgaccgct	gtaccacccc	ancatgttct	gcgcggcgcg	480
agggcaagac	cagaaggact	cctgcaacgt	gagagagggg	aaaggggagg	gcaggcgact	540
cagggaagg	tggagaagg	ggagacagag	acacacaggg	ccgcatggcg	agatgcagag	600
atggagagac	acacagggag	acagtgacaa	ctagagagag	aaactgagag	aaacagagaa	660
ataaacacag	gaataaagag	aagcaaaagg	agagagaaac	agaaacagac	atggggaggc	720
agaaacacac	acacatagaa	atgcagttga	ccttccaaca	gcatggggcc	tgagggcggg	780
gacctccacc	caatagaaaa	tcctcttata	acttttgact	ccccaaaaac	ctgactagaa	840
atagcctact	gttgacgggg	agccttacca	ataacataaa	tagtgcattt	atgcatacgt	900
tttatgcatt	catgatatac	ctttgttgga	attttttgat	atttctaagc	tacacagttc	960
gtctgtgaat	ttttttaaat	tgttgcaact	ctcctaaaaa	ttttctgatg	tgtttattga	1020
aaaaatccaa	gtataagtgg	acttgtgcat	tcaaacagg	gttgttcaag	ggccaactgt	1080
gtaccagag	ggaaacagtg	acacagattc	atagaggtga	aacacgaaga	gaaacaggaa	1140
aaatcaagac	tctacaaaga	ggctgggcag	gggtggtcat	gcctgtaatc	ccagcacttt	1200
gggaggcgag	gcaggcagat	cacttgaggt	aaggagttca	agaccagcct	ggccaaaatg	1260
gtgaaatcct	gtctgtacta	aaaatacaaa	agttagctgg	atatgggtgg	aggcgccgtg	1320
aatccagct	acttgggagg	ctgaggcagg	agaattgctt	gaatatggga	ggcagaggtt	1380
gaagtgaagt	gagatcacac	cactatactc	cagctggggc	aacagagtaa	gactctgtct	1440
caaaaaaaaa	aaaaaaaaaa					1459

<210> 175

<211> 1167

<212> DNA

<213> Homo sapien

<220>

<221> misc\_feature

<222> (1)...(1167)

<223> n = A,T,C or G

<400> 175

gcgcagccct	ggcaggcggc	actgggtcatg	gaaaacgaat	tgttctgctc	gggcgtcctg	60
gtgcatccgc	agtgggtgct	gtcagccgca	cactgtttcc	agaactccta	caccatcggg	120
ctgggcctgc	acagtcttga	ggccgaccaa	gagccaggga	gccagatggg	ggaggccagc	180
ctctccgtac	ggcaccacga	gtacaacaga	ctcttgctcg	ctaaccgacct	catgctcatc	240
aagttggacg	aatccgtgtc	cgagtctgac	accatccgga	gcatcagcat	tgcttcgcag	300
tgccctaccg	cggggaactc	ttgcctcgtn	tctggctggg	gtctgctggc	gaacggcaga	360
atgcctaccg	tgtgcaactg	cgtgaacgtg	tcgggtgggt	ctgaggangt	ctgcagtaag	420
ctctatgacc	cgctgtacca	ccccagcatg	ttctgcgccg	gcggagggca	agaccagaag	480
gactcctgca	acgggtgactc	tggggggccc	ctgatctgca	acgggtactt	gcagggcctt	540
gtgtctttcg	gaaaagcccc	gtgtggccaa	cttggcgtgc	caggtgtcta	caccaacctc	600
tgcaaattea	ctgagtggat	agagaaaacc	gtccagncca	gttaactctg	gggactggga	660
acccatgaaa	ttgaccccc	aatacatcct	gcggaangaa	ttcaggaata	tctgttccca	720
gcccctcctc	cctcaggccc	aggagtccag	gccccagccc	cctcctccct	caaaccaagg	780

```

gtacagatcc ccagcccccctc ctccctcaga cccaggagtc cagacccccc agcccccctc 840
ccttcagacc caggagtcca gcccctcctc cttcagacgc aggagtccag acccccacgc 900
ccttcctccg tcagaccacag ggggtgcagge ccccaacccc tcttcctca gagtccagagg 960
tccagcccc caacccctcg ttccccagac ccagagggtnc aggtcccagc ccttcctccc 1020
tcagaccacg cgggtccaatg ccacctagan tttccctgta cacagtcccc ccttggtggca 1080
tttgaccaca accttaccag ttgggttttc attttttgc cctttccct agatccagaa 1140
ataaagtnta agagaagcgc aaaaaaa 1167

```

&lt;210&gt; 176

&lt;211&gt; 205

&lt;212&gt; PRT

&lt;213&gt; Homo sapien

&lt;220&gt;

&lt;221&gt; VARIANT

&lt;222&gt; (1)...(205)

&lt;223&gt; Xaa = Any Amino Acid

&lt;400&gt; 176

```

Met Glu Asn Glu Leu Phe Cys Ser Gly Val Leu Val His Pro Gln Trp
 1          5          10          15
Val Leu Ser Ala Ala His Cys Phe Gln Asn Ser Tyr Thr Ile Gly Leu
 20          25          30
Gly Leu His Ser Leu Glu Ala Asp Gln Glu Pro Gly Ser Gln Met Val
 35          40          45
Glu Ala Ser Leu Ser Val Arg His Pro Glu Tyr Asn Arg Leu Leu Leu
 50          55          60
Ala Asn Asp Leu Met Leu Ile Lys Leu Asp Glu Ser Val Ser Glu Ser
 65          70          75          80
Asp Thr Ile Arg Ser Ile Ser Ile Ala Ser Gln Cys Pro Thr Ala Gly
 85          90          95
Asn Ser Cys Leu Val Ser Gly Trp Gly Leu Leu Ala Asn Gly Arg Met
100          105          110
Pro Thr Val Leu His Cys Val Asn Val Ser Val Val Ser Glu Xaa Val
115          120          125
Cys Ser Lys Leu Tyr Asp Pro Leu Tyr His Pro Ser Met Phe Cys Ala
130          135          140
Gly Gly Gly Gln Asp Gln Lys Asp Ser Cys Asn Gly Asp Ser Gly Gly
145          150          155          160
Pro Leu Ile Cys Asn Gly Tyr Leu Gln Gly Leu Val Ser Phe Gly Lys
165          170          175
Ala Pro Cys Gly Gln Leu Gly Val Pro Gly Val Tyr Thr Asn Leu Cys
180          185          190
Lys Phe Thr Glu Trp Ile Glu Lys Thr Val Gln Xaa Ser
195          200          205

```

&lt;210&gt; 177

&lt;211&gt; 1119

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 177

```

ggcgaactgc agccctggca ggcggcactg gtcattgaaa acgaattggt ctgctcgggc 60
gtccctgggtgc atccgcagtg ggtgctgtca gccgcacact gtttcacagaa ctccacaccc 120
atcgggcttg gctgcacag tcttgaggcc gaccaagagc cagggagcca gatggtggag 180
gccagcctct ccgtacggca cccagagtac aacagaccct tgctcgttaa cgacctcatg 240
ctcatcaagt tggacgaatc cgtgtccgag tctgacacca tccggagcat cagcattgct 300
tcgcagtgcc ctaccgcggg gaactcttgc ctggtttctg gctggggtct gctggcgaac 360

```

```

gatgctgtga ttgccatcca gtcccagact gtgggagggt gggagtgtga gaagctttcc 420
caaccctggc aggggtgtac catttcggca acttccagt caaggacgtc ctgctgcatc 480
ctcactgggt gctcactact gctcactgca tccccggaa cactgtgatc aactagccag 540
caccatagtt ctccgaagtc agactatcat gattactgtg ttgactgtgc tgtctattgt 600
actaaccatg ccgatgttta ggtgaaatta gcgtcacttg gcctcaacca tcttggtatc 660
cagttatcct cactgaattg agatttcctg cttcagtgtc agccattccc acataatttc 720
tgacctacag aggtgaggga tcatatagct ctccaaggat gctgggtactc ccctcacaaa 780
ttcattttctc ctgtttagt gaaagggtgc cctctggag cctcccaggg tgggtgtgca 840
ggtcacaatg atgaatgtat gatcgtgttc ccattaccca aagcctttaa atccctcatg 900
ctcagtacac cagggcaggt ctagcatttc ttcatttagt gtatgctgtc cattcatgca 960
accacctcag gactcctgga ttctctgcct agttgagctc ctgcatgctg cctccttggg 1020
gaggtgaggg agagggccca tggttcaatg ggatctgtgc agttgtaaca cattaggtgc 1080
ttaataaaca gaagctgtga tgtaaaaaa aaaaaaaaa 1119

```

<210> 178  
 <211> 164  
 <212> PRT  
 <213> Homo sapien

<220>  
 <221> VARIANT  
 <222> (1)...(164)  
 <223> Xaa = Any Amino Acid

<400> 178

Met	Glu	Asn	Glu	Leu	Phe	Cys	Ser	Gly	Val	Leu	Val	His	Pro	Gln	Trp
1				5					10					15	
Val	Leu	Ser	Ala	Ala	His	Cys	Phe	Gln	Asn	Ser	Tyr	Thr	Ile	Gly	Leu
			20					25					30		
Gly	Leu	His	Ser	Leu	Glu	Ala	Asp	Gln	Glu	Pro	Gly	Ser	Gln	Met	Val
		35				40						45			
Glu	Ala	Ser	Leu	Ser	Val	Arg	His	Pro	Glu	Tyr	Asn	Arg	Pro	Leu	Leu
	50				55						60				
Ala	Asn	Asp	Leu	Met	Leu	Ile	Lys	Leu	Asp	Glu	Ser	Val	Ser	Glu	Ser
65				70					75					80	
Asp	Thr	Ile	Arg	Ser	Ile	Ser	Ile	Ala	Ser	Gln	Cys	Pro	Thr	Ala	Gly
			85					90						95	
Asn	Ser	Cys	Leu	Val	Ser	Gly	Trp	Gly	Leu	Leu	Ala	Asn	Asp	Ala	Val
			100					105					110		
Ile	Ala	Ile	Gln	Ser	Xaa	Thr	Val	Gly	Gly	Trp	Glu	Cys	Glu	Lys	Leu
		115				120					125				
Ser	Gln	Pro	Trp	Gln	Gly	Cys	Thr	Ile	Ser	Ala	Thr	Ser	Ser	Ala	Arg
	130				135					140					
Thr	Ser	Cys	Cys	Ile	Leu	Thr	Gly	Cys	Ser	Leu	Leu	Leu	Thr	Ala	Ser
145				150						155				160	
Pro	Gly	Thr	Leu												

<210> 179  
 <211> 250  
 <212> DNA  
 <213> Homo sapien

<400> 179

```

ctggagtgcc ttggtgtttc aagcccctgc aggaagcaga atgcaccttc tgaggcacct 60
ccagctgccc ccggccgggg gatgcgaggc tcggagcacc cttgcccggc tgtgattgct 120
gccaggcaact gttcatctca gcttttctgt ccctttgtct ccggcaagcg cttctgtctga 180
aagttcatat ctggagcctg atgtcttaac gaataaaggt cccatgctcc acccgaaaaa 240

```

atgagagagag

250

<210> 180  
 <211> 202  
 <212> DNA  
 <213> Homo sapien

<400> 180  
 actagtcacag tgtgggtggaa ttccattgtg ttgggcccac cacaatgggt acctttaaca 60  
 tctccacagac ccgcgccttg ccggtgcccc acgtgctgc taacgacagt atgatgctta 120  
 ctgtgctact cggaaactat ttttatgtaa ttaatgtatg ctttcttggt tataaatgcc 180  
 taatttcaaa aaaaaaaaaa aa 202

<210> 181  
 <211> 558  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(558)  
 <223> n = A,T,C or G

<400> 181  
 tccytgtgkt naggttttkg agacamccck agacctwaan ctgtgtcaca gacttcyngg 60  
 aatgttttagg cagtgcctagt aatttcytcg taatgattct gttattactt tccnattct 120  
 ttattcctct ttcttctgaa gattaatgaa gttgaaaatt gaggtggata aatacaaaaa 180  
 ggtagtgatga tagtataagt atctaagtc agatgaaagt gtgttatata tatccattca 240  
 aaattatgca agttagtaat tactcagggt taactaaatt actttaatat gctgttgaac 300  
 ctactctggt ccttggtcag aaaaaattat aaacaggact ttgttagttt gggaagccaa 360  
 attgataata ttctatgttc taaaagtgtg gctatacata aattattaag aaatatggaw 420  
 ttttattccc aggaatatgg kgttcatttt atgaatatta cscrggatag awgtwtgagt 480  
 aaaaacagtt ttggtwaata ygtwaatatg tcmataataa acaakgcttt gacttatttc 540  
 caaaaaaaaa aaaaaaaaa 558

<210> 182  
 <211> 479  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(479)  
 <223> n = A,T,C or G

<400> 182  
 acugggwttk grggatgcta agsccccrga rwtggtttga tccaacctg gcttwttttc 60  
 agaggggaaa atggggccta gaagttacag mscatytagy tgggtgcgmitg gcacctctgg 120  
 cstcacacag astcccgagt agctgggact acaggcacac agtcactgaa gcaggccctg 180  
 ttwgcaattc acgttgccac ctccaactta aacattcttc atatgtgatg tcccttagtca 240  
 ctaagggttaa actttccac ccagaaaagg caacttagat aaaatcttag agtactttca 300  
 tactmttcta agtcctcttc cagcctcact kkgagtcctm cytggggggt gataggaant 360  
 ctctcttggc tttctcaata aartctctat ycatctcatg ttttaatttg tacgcataa 420  
 awtgstgata aaattaaaat gttctggtty mactttaaaa aaaaaaaaaa aaaaaaaaaa 479

<210> 183  
 <211> 384  
 <212> DNA

<213> Homo sapien

<400> 183

```

aggcgggagc agaagctaaa gccaaagccc aagaagagtg gcagtgccag cactggtgcc      60
agtaccagta ccaataacag tgccagtgcc agtgccagca ccagtgggtg cttcagtgct      120
ggtgccagcc tgaccgccac tctcacattt gggctcttcg ctggccttgg tggagctggt      180
gccagcacca gtggcagctc tgggtgcctgt ggtttctcct acaagtgaga ttttagatat      240
tgtaaatcct gccagtcttt ctcttcaagc caggggtgcat cctcagaaac ctactcaaca      300
cagcactcta ggcagccact atcaatcaat tgaagttgac actctgcatt aratctattt      360
gccatttcaa aaaaaaaaaa aaaa                                     384

```

<210> 184

<211> 496

<212> DNA

<213> Homo sapien

<220>

<221> misc\_feature

<222> (1)...(496)

<223> n = A,T,C or G

<400> 184

```

accgaattgg gaccgctggc ttataagcga tcatgttynt ccrgtatkac ctcaacgagc      60
agggagatcg aqtctatacg ctgaagaaat ttgaccgat gggacaacag acctgctcag      120
cccatcctgc tcggttctcc ccagatgaca aatactctsg acaccgaatc accatcaaga      180
aacgcttcaa ggtgctcatg acccagcaac cgcgccttgt cctctgaggg tcccttaaac      240
tgatgtcttt tctgccacct gttacccctc ggagactcgg taaccaaact cttcggactg      300
tgagccctga tgcctttttg ccagccatac tctttggcat ccagtctctc gtggcgattg      360
attatgcttg tgtgaggcaa tcatgggtgg atcaccata aagggaacac atttgacttt      420
tttttctcat attttaaat actacmagaw tattwmagaw waaatgawtt gaaaaactst      480
taaaaaaaaa aaaaaa                                           496

```

<210> 185

<211> 384

<212> DNA

<213> Homo sapien

<400> 185

```

gctggtagcc tatggcgkgg cccacggagg ggtcctgag gccacggrac agtgacttcc      60
caagtatcyt ggcsgcgctc ttctaccgtc cctacctgca gatcttcggg cagattcccc      120
aggaggacat ggacgtggcc ctcatggagc acagcaactg ytcgtcggag cccggttct      180
gggcacaccc tctgggggcc caggcgggca cctgcgtctc ccagtatgcc aactggctgg      240
tggtgctgct cctcgtcate ttctgctcog tggccaacat cctgctggtc aacttgctca      300
ttgccatgtt cagttacaca ttcggaag tacagggcaa cagcgatctc tactgggaag      360
gcgcagcgtt accgcctcat ccgg                                     384

```

<210> 186

<211> 577

<212> DNA

<213> Homo sapien

<220>

<221> misc\_feature

<222> (1)...(577)

<223> n = A,T,C or G

<400> 186

```

gagttagctc ctccacaacc ttgatgaggt cgtctgcagt ggctctctgc ttcataccgc      60

```



```

tncatcgctc atactgtagg tttgccacca cytcctggca tcttggggcg gontaatatt 120
ccaggaaact ctcaatcaag tcaccgtcga tgaaacctgt gggctgggtc tgtcttcgcg 180
tctgtgtgaa aggatctccc agaaggagtg ctcgatcttc ccacacttt tgatgacttt 240
tttgagtcga ttctgcatgt ccagcaggag gttgtaaccag ctctctgaca gtgaggtcac 300
cagccctatc atgccgttga mcgtgccgaa garcaaccag ccttgtgtgg gggkkgaagt 360
ctcaaccaga ttctgcatta ccagagagcc gtggcaaaaag acattgacaa actcgcccag 420
gtcaaaaaaag amcamctcct ggargtgctn gccgctcctc gtcmgttggg ggcagcgctw 480
tctttttgac acacaaacaa gttaaaggca ttttcagecc ccagaaantt gtcatcatcc 540
aagatntcgc acagcactna tccagttggg attaaat 577

```

&lt;210&gt; 187

&lt;211&gt; 534

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; (1)...(534)

&lt;223&gt; n = A,T,C or G

&lt;400&gt; 187

```

aacatcttcc tgtataatgc tgtgtaatat cgatccgath ttgtctgstg agaatyctw 60
actkggaaaa gmaacattaa agcctggaca ctggtattaa aattcacaat atgcaacact 120
ttaaaccagt tgtcaatctg ctcccyynac tttgtcatca ccagtctggg aakaagggtg 180
tgccttattc acacctgtta aaagggcgct aagcattttt gattcaacat cttttttttt 240
gacacaagtc cgaaaaaagc aaaagtaaac agttatyaat ttgttagcca attcactttc 300
ttcatgggac agagccatyt gatttaaaaa gcaaattgca taatattgag ctyggggagc 360
tgatatttga gcggaagagt agcctttcta cttcaccaga cacaactccc ttcatattg 420
ggatgttnac naaagtwaig tctctwacag atgggatgct tttgtggcaa tttctgtctg 480
aggatctccc agtttatita ccacttgcac aagaaggcgt tttcttctc aggc 534

```

&lt;210&gt; 188

&lt;211&gt; 761

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; (1)...(761)

&lt;223&gt; n = A,T,C or G

&lt;400&gt; 188

```

agaaaccagt atctctnaaa acaacctctc ataccttgtg gacctaatth tgtgtgcgtg 60
tgtgtgtgcg cgcataattat atagacagge acatcttttt tacttttgta aaagcttatg 120
ctcttttggg atctatatct gtgaaagttt taatgatctg ccataatgtc ttggggacct 180
ttgtcttctg tgtaaattgg actagagaaa acacctatnt tatgagtcaa tctagtngt 240
ttttattcga atgaaggaaa tttccagatn acaacactna caaactctcc ctkgackarg 300
ggggacaaaag aaaagcaaaa ctgamcataa raaacaatwa cctggtgaga arttgcataa 360
acagaaaatw ggtagtatat tgaarnacag catcattaaa rmgttwtktt wttctccctt 420
gcaaaaaaca tgtaacngact tcccgttgag taatgccaa gttgtttttt tatnataaaa 480
cttgcccttc attacatggt tnaaagtggg gtgggtgggc aaaatattga aatgatggaa 540
ctgactgata aagctgtaca aataagcagt gtgcctaaca agcaacacag taatgttgac 600
atgcttaatt cacaaatgct aatttcatta taaatgtttg ctaaaatata ctttgaacta 660
ttttctgtgn ttcccagagc tgagatntta gattttatgt agtatnaagt gaaaaantac 720
gaaaataata acattgaaga aaananaaaa aaanaaaaaa a 761

```

&lt;210&gt; 189

&lt;211&gt; 482

<212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(482)  
 <223> n = A,T,C or G

<400> 189  
 tttttttttt tttgccgatn ctactatttt attgcaggan gtgggggtgt atgcaccgca 60  
 caccggggct atnagaagca agaaggaagg agggagggca cagccccttg ctgagcaaca 120  
 aagccgectg ctgccttctc tgtctgtctc ctgggtgcagg cacatgggga gaccttcccc 180  
 aaggcagggg ccaccagtcc aggggtggga atacaggggg tgggagtgt gcataagaag 240  
 tgataggcac aggccacccg gtacagaccc ctcggtcctt gacaggtnga tttcgaccag 300  
 gtcattgtgc cctgcccagg cacagcgtn atctggaaaa gacagaatgc tttccttttc 360  
 aaatttggtc ngtcattngaa ngggcanttt tccaanttng gctnggtctt ggtacncttg 420  
 gttcgcccca gctccnctg caaaaantat tcaccnctt cnaattgct tgcnggnccc 480  
 cc 482

<210> 190  
 <211> 471  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(471)  
 <223> n = A,T,C or G

<400> 190  
 tttttttttt ttttaaaaca gtttttcaca acaaaattta ttagaagaat agtggttttg 60  
 aaaactctcg catccagtga gaactacat acaccacatt acagctngga atgtntctca 120  
 aatgtctggt caaatgatac aatggaacca ttcaatctta cacatgcacg aaagaacaag 180  
 cgcttttgac atacaatgca caaaaaaaaa aggggggggg gaccacatgg attaaaattt 240  
 taagtactca tcacatacat taagacacag ttctagtcca gtcnaaaatc agaactgcnt 300  
 tgaaaaattt catgtatgca atccaaccaa agaacttnat tggatgatcat gantnctcta 360  
 ctacatcnac cttgatcatt gccaggaacn aaaagttnaa ancacnctg acaaaaanaa 420  
 tctgtaattn anttcaacct ccgtacngaa aaatnttntt tatacactcc c 471

<210> 191  
 <211> 402  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(402)  
 <223> n = A,T,C or G

<400> 191  
 gagggattga aggtctgttc tastgtcggm ctgttcagcc accaactcta acaagttgct 60  
 gtcttccact cactgtctgt aagcttttta acccagacwg tatcttcata aatagaacaa 120  
 attcttcacc agtcacatct tctaggacct ttttggtatc agttagtata agctcttcca 180  
 cttcctttgt taagacttca tctggtaaaag tcttaagtgt tgtagaaagg aattyaattg 240  
 ctggttctct aacaatgtcc tctccttgaa gtatttggct gaacaacca cctaaagtcc 300  
 ctttgtgcat ccatttttaa tatacttaat agggcattgk tncactaggt taaattctgc 360  
 aagagtcate tgtctgcaaa agttgcgtta gtatatctgc ca 402

<210> 192  
 <211> 601  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(601)  
 <223> n = A,T,C or G

<400> 192  
 gagctcggat ccaataatct ttgtctgagg gcagcacaca tatncagtgc catggnaact 60  
 ggtctacccc acatgggagc agcatgccgt agntatataa ggtcattccc tgagtcagac 120  
 atgcytyttt gaytaccgtg tgccaagtgc tggtgattct yaacacacyt ccatcccgyt 180  
 cttttgtgga aaaactggca cttktctgga actagcarga catcacttac aaattcaccc 240  
 acgagacact tgaaagggtg aacaaagcga yctttgcatt gctttttgtc cctccggcac 300  
 cagttgtcaa tactaaccog ctggtttgcc tccatcacat ttgtgatctg tagctctgga 360  
 tacatctcct gacagtactg aagaacttct tcttttgttt caaaagcacc tcttggtgcc 420  
 tgttggtatca gggtcccatt tcccagtcyg aatgttcaca tggcatattt wacttcccac 480  
 aaaaatttgc gatttgaggc tcagcaacag caaatcctgt tccggcattg gctgcaagag 540  
 cctcgatgta gccggccagc gccaaaggcag gcgccgtgag ccccaccagc agcagaagca 600  
 g 601

<210> 193  
 <211> 608  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(608)  
 <223> n = A,T,C or G

<400> 193  
 atacagccca nateccacca cgaagatgcg cttgttgact gagaacctga tgcgggtcact 60  
 ggtcccgtg tagccccagc gactctccac ctgctggaag cggttgatgc tgcactcytt 120  
 cccaacgcag gcagmagcgg gscgggtcaa tgaactccay tctgtggttg gggtkgacgg 180  
 tkaagtgcag gaagaggctg accacctcgc ggtccaccag gatgccgac tgtgeggagc 240  
 ctgcagcgaa actcctcgat ggcatgagc gggaagcgaa tgaggcccag ggccttgccc 300  
 agaaccttcc gctgtttctc tggcgtcacc tgcagctgct gccgtgaca ctgggctctg 360  
 gaccagcgga caaacggcrt tgaacagccg caacctcagg atgccagtg tgtcgcgctc 420  
 caggammgsc accagcgtgt ccaggccaat gtcgggtgaag cctccgcgg gtrattggcgt 480  
 ctgcagtggt tttgtcgatg ttctccaggc acaggtggc cagctgcggt tcatcgaaga 540  
 gtcgcgctg cgtgagcagc atgaaggcgt tgtcggtctg cagttcttct tcaggaaactc 600  
 cagccaat 608

<210> 194  
 <211> 392  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(392)  
 <223> n = A,T,C or G

<400> 194  
 gaacggctgg accttgctc gcattgtgct tgctggcagg gaataccttg gcaagcagyt 60

```

ccagtcgag cagccccaga ccgctgccgc ccgaagctaa gcctgcctct ggccctcccc 120
tccgcctcaa tgcagaacca gtagtgggag cactgtgttt agagttaaga gtgaacactg 180
tttgatttta ctggggaatt tcctctgtta tatagctttt cccaatgcta atttccaaac 240
aacaacaaca aaataacatg tttgcctgtt aagttgtata aaagtaggtg attctgtatt 300
taaagaaaat attactgtta catatactgc ttgcaatttc tgtatttatt gktnctstgg 360
aaataaatat agttattaaa ggttgtcant cc 392

```

<210> 195

<211> 502

<212> DNA

<213> Homo sapien

<220>

<221> misc\_feature

<222> (1)...(502)

<223> n = A,T,C or G

<400> 195

```

ccsttkgagg ggtkaggkyc cagttyccga gtggaagaaa caggccagga gaagtgcgtg 60
ccgagctgag gcagatgttc ccacagtgc cccagagacc stgggstata gtytctgacc 120
cctcncaagg aaagaccacs ttctggggac atgggctgga gggcaggacc tagaggcacc 180
aagggaaggc cccattccgg ggstgttccc cgaggaggaa ggggaagggc tctgtgtgcc 240
ccccasgagg aagaggccct gagtcctggg atcagacacc ccttcacgtg tatccccaca 300
caaatgcaag ctcaccaagg tccccctcga gtccccctcc stacaccctg amcggccact 360
gscscacacc caccagagc acgccacccg ccattggggar tgtgctcaag gartcgcnng 420
gcarcgtgga catctngtcc cagaaggggg cagaatctcc aatagangga ctgarcmstt 480
gctnanaaaa aaaaanaaaa aa 502

```

<210> 196

<211> 665

<212> DNA

<213> Homo sapien

<220>

<221> misc\_feature

<222> (1)...(665)

<223> n = A,T,C or G

<400> 196

```

ggttacttgg tticattgcc accacttagt ggatgtcatt tagaaccatt ttgtctgctc 60
cctctggaag ccttgccgag agcggacttt gtaattgttg gagaataact gctgaatttt 120
wagctgtttk gagttgatts gcaccactgc acccacaact tcaatatgaa aacyawttga 180
actwatttat tatcttgtga aaagtataac aatgaaaatt ttgttcatac tgtattkac 240
aagtatgatg aaaagcaawa gatatatatt cttttattat gttaaattat gattgccatt 300
attaatcggc aaaatgtgga gtgtatgttc ttttcacagt aatatatgcc ttttgtaact 360
tcacttggtt attttattgt aaatgartta caaaattcct aatttaagar aatggatgt 420
watatttatt tcattaattt ctttcctkgt ttacgtwaat tttgaaaaga wtgcatgatt 480
tcttgacaga aatcgatctt gatgctgtgg aagtagtttg acccacatcc ctatgagttt 540
ttcttagaat gtataaagggt tgtagcccat cnaacttcaa agaaaaaaat gaccacatac 600
tttgcaatca ggctgaaatg tggcatgctn ttctaattcc aactttataa actagcaaan 660
aagt 665

```

<210> 197

<211> 492

<212> DNA

<213> Homo sapien

<220>

<221> misc\_feature  
 <222> (1)...(492)  
 <223> n = A,T,C or G

<400> 197  
 ttttnttttt ttttttttgc aggaaggatt ccatitattg tggatgcatt ttcacaatat 60  
 atgtttattg gagcgatcca ttatcagtga aaagtatcaa gtgtttataa natttttagg 120  
 aaggcagatt cacagaacat gctngtcngc ttgcagtttt acctcgtana gatnacagag 180  
 aatttatagtc naaccagtaa acnaggaatt tactttttcaa aagattaaat ccaaactgaa 240  
 caaaattcta ccttgaaact tactccatcc aaatatggga ataanagtca gcagtgatac 300  
 attctcttct gaacttttaga ttttctagaa aaatatgtaa tagtgatcag gaagagctct 360  
 tgttcaaaag tacaacnaag caatgttccc ttaccatagg ccttaattca aactttgatc 420  
 catttcactc ccatcacggg agtcaatgct acctgggaca cttgtatttt gtatcatnctg 480  
 ancntggcct aa 492

<210> 198  
 <211> 478  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(478)  
 <223> n = A,T,C or G

<400> 198  
 tttnttttgn atttcantct gtannaanta ttttcattat gtttattana aaaatatnaa 60  
 tgtntccach acaaatcatn ttacntnagt aagaggccan ctacattgta caacatacac 120  
 tgagtatat ttgaaaagga caagtttaaa gtanacncat attgccganc atancacatt 180  
 tatacatggc ttgattgata tttagcacag canaaaactga gtgagttacc agaaanaaat 240  
 natatatgtc aatcngattt aagatacaaa acagatccta tgggtacatan catcntgtag 300  
 gagtttgtgc tttatgttta ctgaaagtca atgcagttcc tgtacaaaga gatggccgta 360  
 agcattctag tacctctact ccatgggtta gaatcgtaca cttatgttta catatgtnc 420  
 gggttaagaat tgtgttaagt naanttatgg agaggtccan gagaaaaatt tgatncaa 478

<210> 199  
 <211> 482  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(482)  
 <223> n = A,T,C or G

<400> 199  
 agtgacttgt cctccaacaa aaccccttga tcaagtttgt ggcactgaca atcagacct 60  
 tgctagttcc tgtcatctat tgcctactaa atgcagactg gaggggacca aaaaggggca 120  
 tcaactccag ctggattatt ttggagcctg caaatctatt cctacttgta cggactttga 180  
 agtgattcag tttcctctac ggatgagaga ctggctcaag aatatcctca tgcagcttta 240  
 tgaagccnac tctgaacacg ctggttatct nagatgagaa ncagagaaat aaagtcnaga 300  
 aaatttacct ggangaaaag aggccttngg ctggggacca tccattgaa ccttctctta 360  
 anggacttta agaanaaact accacatgtn tgtngtatcc tggtgccngg ccgtttantg 420  
 aacntngacn ncacccctnt ggaatanant cttgacngcn tcctgaactt gctcctctgc 480  
 ga 482

<210> 200  
 <211> 270



<213> Homo sapien

<220>

<221> misc\_feature

<222> (1)...(583)

<223> n = A,T,C or G

<400> 203

tttttttttt	ttttttttga	ccccctctt	ataaaaaaca	agttaccatt	ttattttact	60
tacacatatt	tattttataa	ttggtattag	atattcaaaa	ggcagctttt	aaaatcaaac	120
taaaatggaaa	ctgccttaga	tacataattc	ttaggaatta	gcctaaaatc	tgcctaaagt	180
gaaaatcttc	tctagctctt	ttgactgtaa	atttttgact	cttgtaaaac	atccaaattc	240
atttttcttg	tctttaaaat	tatctaattc	ttccattttt	tccctattcc	aagtcaattt	300
gcttctctag	cctcatttcc	tagctcttat	ctactattag	taagtggctt	ttttcctaaa	360
agggaaaaca	ggaagagana	atggcacaca	aaacaaacat	tttatattca	tatttctacc	420
tacgttaata	aaatagcatt	ttgtgaagcc	agctcaaaag	aaggcttaga	tccttttatg	480
tccatttttag	tactataaacg	atatacnaag	tgcagaatg	caaaagggtt	gtgaacattt	540
attcaaaagc	taatataaga	tatttcacat	actcatcttt	ctg		583

<210> 204

<211> 589

<212> DNA

<213> Homo sapien

<220>

<221> misc\_feature

<222> (1)...(589)

<223> n = A,T,C or G

<400> 204

ttttttttnt	tttttttttt	tttttttctc	ttcttttttt	ttganaatga	ggatcgagtt	60
tttcaactctc	tagatagggc	atgaagaaaa	ctcatctttc	cagcttttaa	ataacaatca	120
aatctcttat	gctatatcat	attttaagtt	aaactaatga	gtcactggct	tatcttctcc	180
tgaaggaaat	ctgttcattc	ttctcattca	tatagttata	tcaagtacta	ccttgcatat	240
tgagagggtt	ttcttctcta	tttacacata	tatttccatg	tgaatttgta	tcaaaccctt	300
attttcatgc	aaactagaaa	ataatgtntt	cttttgcata	agagaagaga	acaatatnag	360
cattacaaaa	ctgctcaaat	tgtttggtta	gnttatccat	tataattagt	tnggcaggag	420
ctaatacaaa	tcacattttc	ngacnagcaa	taataaaact	gaagtaccag	ttaaatatcc	480
aaaataatta	aaggaacatt	tttagcctgg	gtataattag	ctaattcact	ttacaagcat	540
ttattnagaa	tgaattcaca	tggtattatt	cctagagcca	acacaatgg		589

<210> 205

<211> 545

<212> DNA

<213> Homo sapien

<220>

<221> misc\_feature

<222> (1)...(545)

<223> n = A,T,C or G

<400> 205

tttttntttt	ttttttcagt	aataatcaga	acaatattta	tttttatatt	taaaattcat	60
aqaaaagtgc	cttacattta	ataaaagttt	gtttctcaaa	gtgatcagag	gaattagata	120
tngtcttgaa	caccaatatt	aatttgagga	aaatacacca	aaatacatta	agtaaattat	180
ttaagatcat	agagcttgta	agtgaaga	taaaatttga	cctcagaaac	tctgagcatt	240
aaaaatccac	tattagcaaa	taaattacta	tggacttctt	gctttaattt	tgtgatgaat	300
atgggggtgc	actggtaaac	caacacattc	tgaaggatac	attacttagt	gatagattct	360

```

tatgtactttt gctanatnac gtggatatga gttgacaagt ttctctttct tcaatctttt 420
aaggggcnaga ngaaatgagg aagaaaagaa aaggattacg catactgttc ttctctatngg 480
aaggattaga tatgtttcct ttgccaatat taaaaaata ataatgttta ctactagtga 540
aacc 545

```

```

<210> 206
<211> 487
<212> DNA
<213> Homo sapien

```

```

<220>
<221> misc_feature
<222> (1)...(487)
<223> n = A,T,C or G

```

```

<400> 206
tttttttttt ttttttagtc aagtttctna tttttattat aattaaagtc ttggtcattt 60
cattttattag ctctgcaact tacatattta aattaaagaa acgttnttag acaactgtna 120
caatttataa atgtaagggtg ccattattga gtanatatat tcctccaaga gtggatgtgt 180
cccttctccc accaactaat gaancagcaa cattagtta attttattag tagatnatac 240
actgctgcaa acgctaattc tcttctccat ccccatgtng atattgtgta tatgtgtgag 300
ttggtnagaa tgcattcanca atctnacaat caacagcaag atgaagctag gcntgggctt 360
tcggtgaaaa tagactgtgt ctgtctgaat caaatgatct gacctatcct cgggtggcaag 420
aactcttcga accgcttcct caaaggcngc tgccacattt gtggcntctn ttgcacttgt 480
ttcaaaa 487

```

```

<210> 207
<211> 332
<212> DNA
<213> Homo sapien

```

```

<220>
<221> misc_feature
<222> (1)...(332)
<223> n = A,T,C or G

```

```

<400> 207
tgaattggct aaaagactgc atttttanaa ctagcaactc ttatttcttt cttttaaaaa 60
tacatagcat taaatcccaa atcctattta aagacctgac agcttgagaa ggtcactact 120
gcattttatag gaccttctgg tggttctgct gttacntttg aantctgaca atccttgana 180
atctttgcat gcagaggagg taaaagggtat tggattttca cagaggaana acacagogca 240
gaaatgaagg ggccaggctt actgagcttg tccactggag ggctcatggg tgggacatgg 300
aaaagaaggc agcctaggcc ctggggagcc ca 332

```

```

<210> 208
<211> 524
<212> DNA
<213> Homo sapien

```

```

<220>
<221> misc_feature
<222> (1)...(524)
<223> n = A,T,C or G

```

```

<400> 208
agggcggtgt gcggagggtg ttactgtttt gtctcagtaa caataaatac aaaaagactg 60
gttgtgttcc ggccccatcc aaccacgaag ttgattttctc ttgtgtgcag agtgactgat 120
tttaaaggac atggagcttg tcacaatgtc acaatgtcac agtgtgaagg gcacactcac 180

```



```

tcccgcggtga ttccacatita gcaaccaaca atagctcatg agtccatact tgtaaatact 240
tttggcagaa taattnttga aacttgcaga tgataactaa gatccaagat atttcccaaa 300
tttaalagaa gtgggtcata atattaatta cctgttcaca tcagcttcca tttaacaagtc 360
ctgagcccag acaactgacat caaactaago ccacttagac tctcaccac cagtctgtcc 420
tgtcatcaga caggaggctg tcaccttgac caaattctca ccagtcaatc atctatccaa 480
caaccattac ctgatccact tccggtaatg caccaccttg gtga 524

```

<210> 209  
 <211> 159  
 <212> DNA  
 <213> Homo sapien

```

<400> 209
gggtgagtaa atccagaggt gccatggaga aaattccagt gtcagcattc ttgctccttg 60
tggcctcttc ctacactctg gccagagata ccacagtcaa acctggagcc aaaaaggaca 120
caaaggactc tggacccaaa ctgcccaga cctctcca 159

```

<210> 210  
 <211> 256  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(256)  
 <223> n = A,T,C or G

```

<400> 210
actccctggc aqacaaaggc agaggagaga gctctgttag ttctgtgttg ttgaactgcc 60
actgaatttc ttccacttg gactattaca tgccanttga gggactaatg gaaaaacgta 120
tggggagatt ttanccaatt tangtntgta aatggggaga ctggggcagg cgggagagat 180
ttgcagggtg naaatgggan ggctggtttg ttanatgaac agggacatag gaggtaggca 240
ccaggatgct aaatca 256

```

<210> 211  
 <211> 264  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(264)  
 <223> n = A,T,C or G

```

<400> 211
acattgtttt tttagataaa agcattgaga gagctctcct taacgtgaca caatggaagg 60
actggaacac ataccacat ctttgttctg agggataatt ttctgataaa gtcttgctgt 120
atattcaagc acatatgtta tatattattc agttccatgt ttatagccta gttaaggaga 180
ggggagatac attcngaaag aggactgaaa gaaatactca agtnggaaaa cagaaaaaga 240
aaaaaaggag caaatgagaa gcct 264

```

<210> 212  
 <211> 328  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature

<222> (1)...(328)

<223> n = A,T,C or G

<400> 212

acccaaaaat ccaatgctga atatttggtc tcattattcc canattcttt gattgtcaaa	60
ggattttaatg ttgtctcagc ttgggcactt cagttaggac ctaaggatgc cagccggcag	120
gtttatataat gcagcaacaa tattcaagcg cgacaacagg ttattgaact tgcccgccag	180
ttnaatttca tccccattga cttgggatcc ttatcatcag ccagagagat tgaaaattta	240
cccctacnac tctttactct ctgganaggg ccagtgggtg tagctataag cttggccaca	300
tttttttttc ctttattcct ttgtcaga	328

<210> 213

<211> 250

<212> DNA

<213> Homo sapien

<220>

<221> misc\_feature

<222> (1)...(250)

<223> n = A,T,C or G

<400> 213

acttatgagc agagcgacat atccnagtgt agactgaata aaactgaatt ctctccagtt	60
taaagcattg ctactgaag ggatagaagt gactgccagg agggaaagta agccaaggct	120
cattatgcc aagganatat acatttcaat tctccaaact tcttctcat tccaagagtt	180
ttcaatattt gcatgaacct gctgataanc catgttaana aacaaatate tctctnacct	240
tctcatcggt	250

<210> 214

<211> 444

<212> DNA

<213> Homo sapien

<220>

<221> misc\_feature

<222> (1)...(444)

<223> n = A,T,C or G

<400> 214

accagaatc caatgctgaa tatttggtt cattattccc agattctttg attgtcaaag	60
gattttaatgt tgtctcagct tgggcacttc agttaggacc taaggatgcc agccggcagg	120
tttatataatg cagcaacaat attcaagcgc gacaacaggc tattgaactt gcccgccagt	180
tgaatttcat tccattgac ttgggatcct tatcatcagc canagagatt gaaaatttac	240
ccctacgact ctttactctc tggagagggc cagtgggtgg agctataagc ttggccacat	300
ttttttttcc ttatttcctt tgtcagagat gcgattcadc catatgctan aaaccaacag	360
agtgactttt acaaaaattcc tataganatt gtgaataaaa ccttacctat agttgccatt	420
actttgctct ccctaataata cctc	444

<210> 215

<211> 366

<212> DNA

<213> Homo sapien

<220>

<221> misc\_feature

<222> (1)...(366)

<223> n = A,T,C or G

<400> 215  
 acctatgagc agagcgacat atccaagtgt anactgaata aaactgaatt ctctccagtt 60  
 taaagcattg ctccactgaag ggatagaagt gactgccagg agggaaaagta agccaaggct 120  
 cattatgcc aagganatat acatttcaat tctccaaact tcttccctcat tccaagagtt 180  
 ttcaatattt gcatgaacct gctgataagc catgttgaga aacaaatata tctctgacct 240  
 tctcatcggt aagcagaggc tgtaggcaac atggaccata gcgaanaaaa aacttagtaa 300  
 tccaagctgt tttctacact gtaaccaggt ttccaaccaa ggtggaaatc tctataact 360  
 ggtgcc 366

<210> 216  
 <211> 260  
 <212> DNA  
 <213> Homo sapien  
 <220>  
 <221> misc\_feature  
 <222> (1)...(260)  
 <223> n = A,T,C or G

<400> 216  
 ctgtataaac agaactccac tgcangaggg agggccgggc caggagaatc tccgcttgtc 60  
 caagacaggg gcctaaggag ggtctccaca ctgctnntaa gggctnttnc atttttttat 120  
 taataaaaag tnnaaaaggc ctcttctcaa cttttttccc ttnggctgga aaatttaaaa 180  
 atcaaaaatt tctnaagtt ntcaagctat catatatact ntatcctgaa aaagcaacat 240  
 aattcttct tccctccttt 260

<210> 217  
 <211> 262  
 <212> DNA  
 <213> Homo sapien  
 <220>  
 <221> misc\_feature  
 <222> (1)...(262)  
 <223> n = A,T,C or G

<400> 217  
 acctacgtgg gtaagtttan aaatgttata atttcaggaa naggaacgca tataattgta 60  
 tcttgccat aattttctat ttttaataagg aaatagcaaa ttgggggtggg gggaatgtag 120  
 ggcattctac agtttgagca aaatgcaatt aaatgtggaa ggacagcact gaaaaatttt 180  
 atgaataatc tgtatgatta tatgtctcta gagtagattt ataattagcc acttaccta 240  
 atatccttca tgcttgtaaa gt 262

<210> 218  
 <211> 205  
 <212> DNA  
 <213> Homo sapien  
 <220>  
 <221> misc\_feature  
 <222> (1)...(205)  
 <223> n = A,T,C or G

<400> 218  
 accaaggtgg tgcattaccg gaantggatc aangacacca tegtggccaa cccctgagca 60  
 ccccatcaaa ctcccttttg tagtaaaactt ggaaccttgg aaatgaccag gccaaagactc 120  
 aggtctcccc agttctactg acctttgtcc ttangntna ngtccaqggg tgctaggaaa 180  
 anaaatcagc agacacaggt gtaaa 205

<210> 219  
 <211> 114  
 <212> DNA  
 <213> Homo sapien

<400> 219  
 tactgtttttg tctcagtaac aataaatata aaaagactgg ttgtgttccg gccccatcca 60  
 accacgaagt tgatttctct tgtgtgcaga gtgactgatt ttaaaggaca tgga 114

<210> 220  
 <211> 93  
 <212> DNA  
 <213> Homo sapien

<400> 220  
 actagccagc acaaaaggca gggtagcctg aattgctttc tgctctttac atttctttta 60  
 aaataagcat ttagtgtcga gtccctactg agt 93

<210> 221  
 <211> 167  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(167)  
 <223> n = A,T,C or G

<400> 221  
 actangtgca ggtgcgcaca aatatttgtc gatattccct tcatcttgga ttccatgagg 60  
 tcttttgccc agcctgtggc tctactgtag taagtttctg ctgatgagga gccagnatgc 120  
 cccccactac ctccctgac gtccccana aatcacccaa cctctgt 167

<210> 222  
 <211> 351  
 <212> DNA  
 <213> Homo sapien

<400> 222  
 agggcggtgt gctggagggcg gtactgacct cattagtagg aggatgcatt ctggcacccc 60  
 gttcttcacc tgtccccaa tccttaaaag gccatactgc ataaagtcaa caacagataa 120  
 atgtttgctg aattaaagga tggatgaaaa aaattaataa tgaatttttg cataatccaa 180  
 ttttctcttt tatatttcta gaagaagttt ctttgagcct attagatccc gggaatcttt 240  
 taggtgagca tgattagaga gcttgtagggt tgccttttaca tatactctggc atatttgagt 300  
 ctggtatcaa aacaatagat tggtaaagggt ggtattattg tattgataag t 351

<210> 223  
 <211> 383  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(383)  
 <223> n = A,T,C or G

<400> 223

```

aaacaaaca aacaaaaaaa acaattcttc attcagaaaa attatcttag ggactgatat      60
tggtaattat ggtcaattta atwrtttkt ggggcatttc ctacattgt cttgacaaga      120
tcaaatgtc tgtgccaaaa ttttgtattt tatttgaga cttcttatca aaagtaatgc      180
tgccaaagga agtctaagga attagtagtg ttcccmcac ttgtttggag tgtgctatct      240
taaaagattt tgatttctcg gaatgacaat tataatttaa ctttggtggg ggaaanagtt      300
ataggaccac agtcttcact tctgatactt gtaaattaat cttttattgc acttggtttg      360
acatttaagc tatatgttta aaa                                     383

```

<210> 224  
 <211> 320  
 <212> DNA  
 <213> Homo sapien

```

<400> 224
cccttgaagg cttcttggtt gaaaatagta cagttacaac caataggaac aacaaaaaga      60
aaaagtttgt gacattgtag tagggagtgt gtacccttta ctcccatca aaaaaaaaaa      120
ggatacatgg ttaaaggata raagggaat attttatcat atgttctaaa agagaaggaa      180
gagaaaatac tactttctcr aaatggaagc ccttaaagggt gctttgatac tgaaggacac      240
aatgtgggac gtccatcttc ctttaragtt gcatgacttg gacacggtaa ctgttgacgt      300
tttaractcm gcattgtgac                                     320

```

<210> 225  
 <211> 1214  
 <212> DNA  
 <213> Homo sapien

```

<400> 225
gaggactgca gccgcgactc gcagccctgg caggcggcac tggtcattga aaacgaattg      60
ttctgtctgg gcgtccctgg gcaccccgag tgggtgtgtg cagccgcaca ctgtttccag      120
aactcctaca ccacggggtt gggcctgcac agtcttgagg ccgaccaaga gccagggagc      180
cagatggttg aggccagcct ctccgtacgg caaccagagt acaacagacc cttgtctgct      240
aacqacctca tgctcatcaa gttggacgaa tccgtgtccg agtctgacac catccggagc      300
atcagcattg cttcgacgtg ccctaccgag gggaaactct gcctcgtttc tggctggggt      360
ctgctggcga acggcagaat gcctaccgtg ctgcagtgcg tgaacgtgtc ggtggtgtct      420
gaggaggtct gcagtaagct ctatgaccog ctgtaccacc ccagcatgtt ctgcgccggc      480
ggagggcaag accagaagga ctctgcaac ggtgactctg gggggccctt gatctgcaac      540
gggtacttgc agggccttgt gtctttcgga aaagccccgt gtggccaagt tggcgtgcca      600
qgtgtctaca ccaacctctg caaattcact gagtggatag agaaaaccgt ccaggccagt      660
taactctggg gactgggaac ccatagaatt gacccccaaa tacatctgct ggaaggaatt      720
caggaatata tgttcccagc cctcctctcc tcaggcccag gattccaggc cccagagccc      780
tctcctctca aaccaagggt acagatcccc agccccctct cctcagacc caggagtcca      840
gacccccagc cccctcctcc ctccagacca ggagtccagc cctcctccc tcagagcccag      900
gagtccagac cccccagccc ctctcctctc agaccagggg gtccaggccc ccaacccctc      960
ctcctcaga ctccagaggtc caagccccc aacctctctt cccagagccc agaggtccag      1020
gtcccagccc ctctcctctc agaccagcg gtccaatgcc acctagactc tccctgtaca      1080
cagtgcctcc ttgtggcacg ttgacccaac cttaccagtt ggtttttcat tttttgtccc      1140
tttcccttag atccagaaat aaagtctaag agaagcgcaa aaaaaaaaaa aaaaaaaaaa      1200
aaaaaaaaaa aaaa                                     1214

```

<210> 226  
 <211> 119  
 <212> DNA  
 <213> Homo sapien

```

<400> 226
atccagtatg tgcagggaga cggaacccca tgtgacagcc cactccacca gggttcccaa      60
agaacctggc ccagtcataa tcattcatcc tgacagtggc aataatcacg ataaccagt      119

```

<210> 227  
 <211> 818  
 <212> DNA  
 <213> Homo sapien

<400> 227  
 acaattcata gggacgacca atgaggacag ggaatgaacc cggctctccc ccagccctga 60  
 tttttgctac atatggggtc ccttttcatt ctttgcaaaa acactgggtt ttctgagaac 120  
 acggacgggtt cttagcaciaa ttgttgaaat ctgtgtaraa ccgggctttg caggggagat 180  
 aattttcctc ctctggagga aagtggtgga ttgacaggca gggagacagt gacaaggcta 240  
 gagaaagcca cgctcggcct tctctgaaac aggatggaac ggcagacccc tgaaaacgaa 300  
 gcttgctccc ttccaatcag ccacttctga gaacccccat ctaacttcc actggaaaag 360  
 agggcctcct caggagcagt ccaagagttt tcaaagataa cgtgacaact accatctaga 420  
 ggaaagggtg caccctcagc agagaagccg agagcttaac tctggctggt tccagagaca 480  
 acctgctggc tgtcttgga tgcgccagc ctttgagagg ccaactaccc atgaacttct 540  
 gccatccact ggacatgaag ctgaggacac tgggcttcaa cactgagttg tcatgagagg 600  
 gacaggctct gccctcaagc cggctgaggg cagcaaccac tctcctccc tttctcacgc 660  
 aaagccattc ccacaaatcc agaccatacc atgaagcaac gagacccaaa cagtttggt 720  
 caagaggata tgaggactgt ctgagcctgg ctttgggctg acaccatgca cacacacaag 780  
 gtccacttct aggttttcag cctagatggg agtcgtgt 818

<210> 228  
 <211> 744  
 <212> DNA  
 <213> Homo sapien

<400> 228  
 actggagaca ctgttgaact tgatcaagac ccagaccacc ccaggtctcc ttctgaggat 60  
 gtcattgacgt ttgacatacc tttggaacga gcctcctcct tggagatgg aagaccgtgt 120  
 tctgtggccga cctggcctct cctggcctgt ttcttaagat gcggagtcac atttcaatgg 180  
 taggaaaagt ggcttcgtaa aatagaagag cagtcactgt ggaactacca aatggcgaga 240  
 tgctcgggtg acattggggt gctttgggat aaaagattta tgagccaact attctctggc 300  
 accagattct aggcagttt gttccactga agclllccc acagcagtc accctctcag 360  
 gctggcagct gaatggcttg ccggtggctc tgtggcaaga tcacactgag atcgatgggt 420  
 gagaaggcta ggatgcttct ctagtgttct tagctgtcac gttggctcct tccaggttg 480  
 ccagacgggtg ttggccactc ccttctaaaa cacaggcgcc ctctgggtga cagtgacccg 540  
 ccgtggatat ccttggccca ttccagcagt ccaggttatg catttcaagt ttggggtttg 600  
 ttcttttctg taatgttcc ctgtgttctg agctgtcttc atttcttggg ctaagcagca 660  
 ttgggagatg tggaccagag atccactcct taagaaccag tggcgaaaga cactttcttt 720  
 cttcactctg aagtagctgg tgg 744

<210> 229  
 <211> 300  
 <212> DNA  
 <213> Homo sapien

<400> 229  
 cgagtctggg ttttgtctat aaagtttgat ccctcctttt ctcatccaaa tcatgtgaac 60  
 cattacacat cgaaataaaa gaaagggtgg agacttgccc aacgccaggc tgacatgtgc 120  
 tgcagggttg ttgtttttta attattattg ttagaaacgt caccacagc ccctgttaat 180  
 ttgtatgtga cagccaactc tgagaaggct ctatttttcc acctgcagag gatccagctc 240  
 cactaggctc ctcttgccc tcacactgga gtctccgcca gtgtgggtgc ccactgacat 300

<210> 230  
 <211> 301  
 <212> DNA  
 <213> Homo sapien

&lt;400&gt; 230

cagcagaaca	aatacaaaata	tgaagagtgc	aaagatctca	taaaatctat	gctgaggaat	60
gagcgacagt	tcaaggagga	gaagcttgca	gagcagctca	agcaagctga	ggagctcagg	120
caatataaag	tcctgggttca	cactcaggaa	cgagagctga	cccagttaag	ggagaagttg	180
cgqgaaggga	gagatgcctc	cctctcattg	aatgagcctc	tccaggccct	cctcaactcg	240
gatgaaccgg	acaagtccca	ggggcaggac	ctccaagaaa	cagacctcgg	ccgcgaccac	300
g						301

&lt;210&gt; 231

&lt;211&gt; 301

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 231

gcaagcacgc	tggcaaatct	ctgtcaggtc	agctccagag	aagccattag	tcatttttagc	60
caggaactcc	aagtccacat	ccttggcaac	tggggacttg	cgcagggttag	ccttgaggat	120
ggcaacacgg	gacttctcat	caggaagtgg	gatgtatgatg	agctgatcaa	gacggccagg	180
tctgaggatg	gcaggatcaa	tgatgtcagg	ccggttggtta	ccgccaatga	tgaacacatt	240
tttttttgtg	gacatgccat	ccatttctgt	caggatctgg	ttgatgactc	ggtcagcagc	300
c						301

&lt;210&gt; 232

&lt;211&gt; 301

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 232

agtaggtatt	tcgtgagaag	ttcaacacca	aaactggaac	atagttctcc	ttcaagtgtt	60
ggcgacagcg	gggttctctg	attctggaat	ataactttgt	gtaaattaac	agccacctat	120
agaagagtcc	atctgctgtg	aaggagagac	agagaactct	gggttccgtc	gtcctgtcca	180
cgtgctgtac	caagtgtctg	tgccagcctg	ttacctgttc	tactgaaaa	tctggctaata	240
gctcttgtgt	atcacttctg	attctgacaa	tcaatcaatc	aatggcctag	agcactgact	300
g						301

&lt;210&gt; 233

&lt;211&gt; 301

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 233

atgactgact	tcccagtaag	gctctctaag	gggtaagtag	gaggatccac	aggatttgag	60
atgctaaggc	cccagagatc	gtttgatcca	accctcttat	tttcagaggg	gaaaatgggg	120
cctagaagtt	acagagcctc	tagctgggtg	gctggcacc	ctggcctcac	acagactccc	180
gagtactggg	gactacaggc	acacagtcac	tgaagcaggc	cctgttagca	attctatgog	240
tacaaattaa	catgagatga	gtagagactt	tattgagaaa	gcaagagaaa	atcctatcaa	300
c						301

&lt;210&gt; 234

&lt;211&gt; 301

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 234

aggctctaca	catcgagact	catccatgat	tgatatgaat	ttaaaaatta	caagcaaaga	60
cattttattc	atcatgatgc	tttcttttgt	ttcttctttt	cgttttcttc	tttttctttt	120
tcaatttcag	caacatactt	ctcaatttct	tcaggattta	aaatcttgag	ggattgatct	180
cgnctcatga	cagcaagttc	aatgtttttg	ccacctgact	gaaccacttc	caggagtgcc	240
ttgatcacca	gcttaatggt	cagatcatct	gcttcaatgg	cttcgtcagt	atagttcttc	300

t 301

<210> 235  
 <211> 283  
 <212> DNA  
 <213> Homo sapien

<400> 235  
 tggggctgtg catcaggcgg gtttgagaaa tattcaattc tcagcagaag ccagaatttg 60  
 aaticcctca tcttttaggg aatcatttac caggtttgga gaggattcag acagctcagg 120  
 tgctttcact aatgtctctg aacttctgtc cctctttgtt catggatagt ccaataaata 180  
 atgttatctt tgaactgatg ctcataggag agaataaag aactctgagt gatatcaaca 240  
 ttagggattc aaagaaatat tagatttaag ctcacactgg tca 283

<210> 236  
 <211> 301  
 <212> DNA  
 <213> Homo sapien

<400> 236  
 aggtcctcca ccaactgcct gaagcacggt taaaattggg aagaagtata gtgcagcata 60  
 aatactttta aatcgatcag atttcctaa cccacatgca atcttcttca ccagaagagg 120  
 tcggagcagc atcatataa ccaagcagaa tgcgtaatag ataaatacaa tggatatatag 180  
 tgggtagacg gcttcatgag tacagtgtac tgtggatcg taatctggac ttgggttgta 240  
 aagcatcgtg taccagtcag aaagcatcaa tactcgacat gaacgaatat aaagaacacc 300  
 a 301

<210> 237  
 <211> 301  
 <212> DNA  
 <213> Homo sapien

<400> 237  
 cagtggtagt ggtggtggac gtggcgttgg tcgtggtgcc ttttttgggtg cccgtcacia 60  
 actcaatttt tgttcgctcc tttttggcct tttccaattt gtccatctca attttctggg 120  
 ccttggttaa tgctcatag taggagtcct cagaccagcc atggggatca aacatatcct 180  
 ttgggtagtt ggtgccaaagc tcgtcaatgg cacagaatgg atcagcttct cgtaaactta 240  
 ggttccgaa attctttctt cctttggata atgtagttca tatccattcc ctcttttatt 300  
 t 301

<210> 238  
 <211> 301  
 <212> DNA  
 <213> Homo sapien

<400> 238  
 gggcagggtt tttttttttt ttttttgatg gtgcagaccc ttgctttatt tgtctgactt 60  
 gttcacagtt cagccccctg ctcaaaaaac caacggggcca gctaaggaga ggaggaggca 120  
 ccttgagact tccggagtcg aggtcttcca gggttcccca gcccatcaat catthtctgc 180  
 accccctgcc tgggaagcag ctccctgggg ggtgggaatg ggtgactaga agggatttca 240  
 gtgtgggacc cagggtctgt tcttcacagt aggaggtgga agggatgact aattttctta 300  
 t 301

<210> 239  
 <211> 239  
 <212> DNA  
 <213> Homo sapien



&lt;400&gt; 239

ataagcagct aggggaattct ttatttagta atgtcctaac ataaaagtgc acataactgc	60
ttctgtcaaa ccatgatact gagctttgtg acaaccacaga aataactaag agaaggcaaa	120
ataataacct tagagatcaa gaaacattta cacagttcaa ctgtttaaaa atagctcaac	180
attcagccag tgagtagagt gtgaatgccg gcatacacag tatacaggtc cttcagggg	239

&lt;210&gt; 240

&lt;211&gt; 300

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 240

ggtcctaattg aagcagcagc ttccacattt taacgcaggt ttacgggtgat actgtccttt	60
gggatctgcc ctccagtggg accttttaag gaagaagtgg gcccaagcta agttccacat	120
gctgggtgag ccagatgact tctgttcctt ggtaactttc ttcaatgggg cgaatggggg	180
ctgccaggtt tttaaaatca tgcctcatct tgaagcacac ggtaacttca cctcctcac	240
gctgtgggtg tactttgatg aaaataccca ctttgttggc ctttctgaag ctataatgtc	300

&lt;210&gt; 241

&lt;211&gt; 301

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 241

gaggtctggt gctgaggtct ctgggctagg aagaggaggt ctgtggagct ggaagccaga	60
cctcttttga ggaaactcca gcagctatgt tgggtgtctt gaggggaatgc aacaaggctg	120
ctcctccatg tattggaaaa ctgcaaaact gactcaactg gaaggaagtg ctgctgccag	180
tgtgaagaac cagcctgagg tgacagaaac ggaagcaaac aggaacagcc agtcttttct	240
tcctcctcct gtcatacggg ctctctcaag catcctttgt tgtcaggggc ctaaaaggga	300
g	301

&lt;210&gt; 242

&lt;211&gt; 301

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 242

cagaggtcct gggatgcaac caatcactct gtttcacgtg actttttatca ccatacaatt	60
tgtggcattt cctcattttc tacattgtag aatcaagagt gtaaataaat gtatatcgat	120
gtcttcaaga atatatcatt cctttttcac tagaaccat tcaaaatata agtcaagaat	180
cttaatatca acaaatatat caagcaaact ggaaggcaga ataactacca taatttagta	240
taagtaccca aagttttata aatcaaaaagc cctaattgata accattttta gaattcaatc	300
a	301

&lt;210&gt; 243

&lt;211&gt; 301

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 243

aggtaagtcc cagtttgaag ctcaaaagat ctggtatgag catagggtca tcgacgacat	60
ggtggcccaa gctatgaaat cagagggagg cttcatctgg gcctgtaaaa actatgatgg	120
tgacgtgcag tcggactctg tggcccaagg gtatggctct ctggcatga tgaccagcgt	180
gctggtttgt ccagatggca agacagtaga agcagaggct gccacaggga ctgtaacccg	240
tcactaccgc atgttccaga aaggacagga gacgtccacc aatccattg cttccatttt	300
t	301

&lt;210&gt; 244

<211> 300  
 <212> DNA  
 <213> Homo sapien

<400> 244  
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 gtcattgcaat cccatttgca ggatctgtct gtgcacatgc ctctgtagag agcagcattc 120  
 ccaggggacct tggaaacagt tgacactgta aggtgcttgc tccccagac acatcctaaa 180  
 aggtgttgta atgggtgaaaa cgtcttcctt ctttattgcc ccttcttatt tatgtgaaca 240  
 actgtttgtc ttttgtgtat cttttttaa ctgtaaaagt caattgtgaa aatgaatatc 300

<210> 245  
 <211> 301  
 <212> DNA  
 <213> Homo sapien

<400> 245  
 gtctgagtat ttaaaatgtt attgaaatta tccccacca atgttagaaa agaaagaggt 60  
 tatatactta gataaaaaat gaggtgaatt actatccatt gaaatcatgc tcttagaatt 120  
 aaggccagga gatattgtca ttaatgtara cttcaggaca ctagagtata gcagccctat 180  
 gttttcaaag agcagagatg caattaaata ttgttttagca tcaaaaaggc cactcaatac 240  
 agctaataaa atgaaagacc taatttctaa agcaattcct tataattttac aaagttttta 300  
 g 301

<210> 246  
 <211> 301  
 <212> DNA  
 <213> Homo sapien

<400> 246  
 ggtctgtcct acaatgcctg cttcttgaaa gaagtoggca ctttctagaa tagctaaata 60  
 acctgggctt attttaaaga actatttgta gtcagattg gttttcctat ggctaaaata 120  
 agtgcctctt gtgaaaalta aataaaacag ttaattcaaa gccttgatat atgttaccac 180  
 taacaatcat actaaatata ttttgaagta caaagtttga catgctctaa agtgacaacc 240  
 caaatgtgtc ttacaaaaca cgttcctaac aaggtatgct ttacactacc aatgcagaaa 300  
 c 301

<210> 247  
 <211> 301  
 <212> DNA  
 <213> Homo sapien

<400> 247  
 aggtcctttg gcagggtcct tggatcagag ctcaaactgg agggaaaggc atttcgggta 60  
 gcctaagagg gcgactggcg gcagcacaac caaggaaggc aaggttggtt cccccacgct 120  
 gtgtcctgtg ttcagggtgcg acacacaatc ctcatgggaa caggatcacc catgcgctgc 180  
 ccttgatgat caaggttggg gcttaagtgg attaaggag gcaagttctg ggttccttgc 240  
 cttttcaaac catgaagtca ggctctgtat ccctcctttt cctaactgat attctaacta 300  
 a 301

<210> 248  
 <211> 301  
 <212> DNA  
 <213> Homo sapien

<400> 248  
 aggtccttgg agatgccatt tcagccgaag gactcttctw ttcggaagta caccctcact 60  
 attaggaaga ttcttagggg taatttttct gaggaaggag aactagccaa ctaagaatt 120

acaggaagaa agtgggttgg aagacagcca aagaaataaa agcagattaa attgtatcag 180  
 gtacattcca gcctgttggc aactccataa aaacatttca gattttaate cogaatttag 240  
 ctactgaac tggatttttg ttttttatgt tgtgtgtcgc agagctaaaa actcagttcc 300  
 ? 301

<210> 249  
 <211> 301  
 <212> DNA  
 <213> Homo sapien

<400> 249  
 gtccagagga agcacctggt gctgaactag gcttgccctg ctgtgaaact gcaettggag 60  
 ccttgacgct gctgttctcc ccgaaaaacc cgaccgacct ccgcgatctc cgtcccggcc 120  
 ccagggagac acagcagtga ctccagagctg gtgcacact gtgcctccct cctcaccgcc 180  
 catcgtaatg aattattttg aaaattaatt ccaaccatct ttcagattct ggatggaaag 240  
 actgaatctt tgactcagaa ttgtttgctg aaaagaatga tgtgacttct ttagtcattt 300  
 a 301

<210> 250  
 <211> 301  
 <212> DNA  
 <213> Homo sapien

<400> 250  
 ggtctgtgac aaggacttgc aggcctgtggg aggcaagtga cctttaacac tacacttctc 60  
 cttatcttta ttggcttgat aaacataatt atttctaaca ctactttatt tccagttgcc 120  
 cataagcaca tcagtacttt tctctggctg gaatagtaaa cttaaagtatg gtacatctac 180  
 ctaaaagact actatgtgga ataatacata ctaatgaagt attacatgat ttaaagacta 240  
 caataaaacc aaacatgctt ataacattaa gaaaaacaat aaagatacat gattgaaacc 300  
 a 301

<210> 251  
 <211> 301  
 <212> DNA  
 <213> Homo sapien

<400> 251  
 gccgaggtcc tacatttggc ccagtttccc cctgcctcct ctccagggcc cctgcctcat 60  
 agacaacctc atagagcata ggagaactgg ttgccctggg gccaggggga ctgtctggat 120  
 gccaggggtc ctcaaaaatg ccaactgtcac tgccaggaaa tgcttctgag cagtacacct 180  
 cattgggac aatgaaaagc ttcaagaaat cttcaggctc actctcttga aggcccgga 240  
 cctctggagg ggggcagtgg aatcccagct ccaggacgga tcctgtcgaa aagatatact 300  
 c 301

<210> 252  
 <211> 301  
 <212> DNA  
 <213> Homo sapien

<400> 252  
 gcaaccaate actctgttct acgtgacttt tatcaccata caatttgtgg catttcctca 60  
 ttttctacat tgtagaatca agagtgtaaa taaatgtata tcgatgtctt caagaatata 120  
 tcaatctttt ttcactagga acccattcaa aatataagtc aagaatctta atatcaacaa 180  
 atatatcaag caaactggaa ggcagaataa ctaccataat ttagtataag taccocaaagt 240  
 tttataaate aaaagcccta atgataacca tttttagaat tcaatcatca ctgtagaato 300  
 a 301

<210> 253

<211> 301  
 <212> DNA  
 <213> Homo sapien

<400> 253  
 ttccctaaga agatgttatt ttgttgggtt ttgttccccc tccatctcga ttctcgtacc 60  
 caactaaaaa aaaaaaataa agaaaaaatg tgctgcgttc tgaaaaataa ctcccttagct 120  
 tggctctgatt gttttcagac cttaaaaatat aaacttggtt cacaagcttt aatccatgtg 180  
 gatttttttt cttagagaac cacaaaacat aaaaggagca agtcggactg aatacctgtt 240  
 tccatagtgc ccacagggtg ttccctcacat tttctccata ggaaaatgct ttttcccaag 300  
 g 301

<210> 254  
 <211> 301  
 <212> DNA  
 <213> Homo sapien

<400> 254  
 cgctgcgcct ttcccttggg ggagggggcaa ggccagaggg ggtccaagtg cagcacgagg 60  
 aacttgacca attcccttga agcgggtggg ttaaaccctg taaatgggaa caaaatcccc 120  
 ccaaattctt tcatcttacc ctgggtggact cctgactgta gaattttttg gttgaaacaa 180  
 gaaaaaaata aagcttttga cttttcaagg ttgcttaaca ggtactgaaa gactggcctc 240  
 acttaactg agccaggaaa agctgcagat ttattaatgg gtgtgttagt gtgcagtgc 300  
 t 301

<210> 255  
 <211> 302  
 <212> DNA  
 <213> Homo sapien

<400> 255  
 agcttttttt tttttttttt tttttttttt ttcattaaaa aatagtgtct tttattataa 60  
 attacigaaa tgtttctttt ctgaatataa atataaatat gtgcaaagtt tgacttggat 120  
 tgggattttg ttgagttctt caagcatctc ctaataccct caagggcctg agtagggggg 180  
 aggaaaaagg actggaggtg gaatctttat aaaaaacaag agtgattgag gcagattgta 240  
 aacattatta aaaaacaaga aacaaacaaa aaaatagaga aaaaaaccac cccaacacac 300  
 aa 302

<210> 256  
 <211> 301  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(301)  
 <223> n = A,T,C or G

<400> 256  
 gttccagaaa acattgaagg tggcttccca aagtctaact agggataccc cctctagcct 60  
 aggaccctcc tccccacacc tcaatccacc aaaccatcca taatgcaccc agataggccc 120  
 acccccaaaa gcttgacac cttgagcaca cagttatgac caggacagac tcatctctat 180  
 aggcaaatag ctgctggcaa actggcatta cctggtttgt ggggatgggg gggcaagtgt 240  
 gtggcctctc ggcttggtta gcaagaacat tcagggtagg cctaagttn tcgtgttagt 300  
 t 301

<210> 257  
 <211> 301

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 257

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gtttgtggagg aactcttggt tgctcattaa gtctactga ttttactat cccctgaatt      60
tccccactta tttttgtctt tcaatategc aggccttaga agaggtctac ctgctccag      120
tcttacctag tccagtctac cccctggagt tagaatggcc atcctgaagt gaaaagtaat      180
gtcacattac tcccttcagt gattttctgt agaagtgcc atcctgaat gccaccaaga      240
tcttaattctt cacatcttta atcttatctc tttgactctt ctttacaccg gagaaggctc      300
c

```

&lt;210&gt; 258

&lt;211&gt; 301

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; (1)...(301)

&lt;223&gt; n = A,T,C or G

&lt;400&gt; 258

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cagcagtagt agatgccgta tgccagcacg cccagcactc ccaggatcag caccagcacc      60
agggggccag ccaccaggcg cagaagcaag ataaacagta ggctcaagac cagagccacc      120
cccagggcaa caagaatcca ataccaggac tggggcaaat cttcaaagat cttaacactg      180
atgtctcggg cattgaggct gtcaataana cgctgatccc ctgctgtatg gtggtgtcat      240
tggtgatccc tgggagcgcc ggtggagtaa cgttgggtcca tggaaagcag cgcccacaac      300
t

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&lt;210&gt; 259

&lt;211&gt; 301

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; (1)...(301)

&lt;223&gt; n = A,T,C or G

&lt;400&gt; 259

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tcatatatgc aaacaaatgc agactangcc tcaggcagag actaaaggac atctcttggg      60
gtgtcctgaa gtgatttgga cccctgaggg cagacacctt agtaggaatc ccagtgggaa      120
gcaaagccat aaggaagccc aggattcctt gtgatcagga agtgggccag gaaggtctgt      180
tccagctcac atctcatctg catgcagcac ggaccggatg cgcccactgg gtcttgctt      240
ccctcccatc ttctcaagca gtgtccttgt tgagccattt gcctccttgg ctccagggtg      300
c

```

&lt;210&gt; 260

&lt;211&gt; 301

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 260

```

ttttttttct cctaaggaa aaagaaggaa caagtctcat aaaaccaa atagcaatggt      60
aaggtgtctt aacttgaaaa agattaggag tcaactggtt acaagttata attgaatgaa      120
agaacigtta cagccacagt tggccatttc atgccaatgg cagcaaaca caggattaac      180
tagggcaaaa taaataagtg tgtggaagcc ctgataagtg cttaataaac agacigaltc      240
actgagacat cagtacctgc cggggcggcc gctcgagccg aattctgcag atatccatca      300

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c

301

<210> 261  
 <211> 301  
 <212> DNA  
 <213> Homo sapien

<400> 261  
 aaatattcga gcaaactctg taactaatgt gtctccataa aaggctttga actcagtga 60  
 tctgcttcca tccacgatc tagcaatgac ctctcggaca tcaaagctcc tcttaagggt 120  
 agcaccaact attccataca attcatcagc aggaaataaa ggctcttcag aagggttcaat 180  
 ggtgacatcc aattttcttct gataatttag attcctcaca acccttctag ttaagtgaag 240  
 ggcatgatga tcatccaaag ccagtggtc acttactcca gactttctgc aatgaagatc 300  
 a 301

<210> 262  
 <211> 301  
 <212> DNA  
 <213> Homo sapien

<400> 262  
 gaggagagcc tggtacagca tttgtaagca cagaatactc caggagtatt tgtaattgtc 60  
 tgtgagcttc ttgccgcaag tctctcagaa atttaaaaag atgcaaattc ctgagtcacc 120  
 cctagacttc ctaaaccaga tcctctgggg ctggaacctg gcactctgca tttgtaatga 180  
 gggctttctg gtgcacacct aattttgtgc atctttgccc taaatcctgg attagtgcc 240  
 catcattacc cccacattat aatgggatag attcagagca gatactctcc agcaaagaat 300  
 c 301

<210> 263  
 <211> 301  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(301)  
 <223> n = A,T,C or G

<400> 263  
 tttagcttgt ggtaaattgac tcacaaaact gatttttaaaa tcaagttaat gtgaattttg 60  
 aaaattacta cttaatccta attcacaata acaatggcat taagggtttga cttgagttgg 120  
 ttcttagtat tatttatggg aaataggctc ttaccacttg caaataactg gccacatcat 180  
 taatgactga cttcccagta aggtctctta aggggtaagt angaggatcc acaggatttg 240  
 agatgctaag gccccagaga tcgtttgatc caaccctctt attttcagag gggaaaatgg 300  
 g 301

<210> 264  
 <211> 301  
 <212> DNA  
 <213> Homo sapien

<400> 264  
 aaagacgtta aaccactcta ctaccaattg tggaactctc aaagggtaaa tgacaaascc 60  
 aatgaatgac tctaaaaaca atattttacat ttaatgggtt gtagacaata aaaaaacaag 120  
 gtggatagat ctagaattgt aacattttta gaaaaccata scatttgaca gatgagaaag 180  
 ctcaattata gatgcaaagt tataactaaa ctactatagt agtaaagaaa tacatttcac 240  
 acccttcata taaatttcaat atcttggett gaggcactcc ataaaatgta tcacgtgcat 300  
 a 301

<210> 265  
 <211> 301  
 <212> DNA  
 <213> Homo sapien

<400> 265  
 tgcctcaagtt atgtgtaagt gtatccgcac ccagaggtaa aactacactg tcctctttgt 60  
 ctctctgtga cgcagtatct cttctctggg gagaagccgg gaagtcttct cctggctcta 120  
 catatctctg gaagtctcta atcaactttt gtccatttg ttctattct tcaggaggga 180  
 ttctcagttt gtcaacatgt tctctaaca cacttgccca ttctgtaaa gaatccaaag 240  
 cagtcctagg ctttgacatg tcaacaacca gcataactag agtatcctc agagatacgg 300  
 c 301

<210> 266  
 <211> 301  
 <212> DNA  
 <213> Homo sapien

<400> 266  
 taccgtctgc ctttctccc atccaggcca tctgogaatc tacatgggtc ctctattctg 60  
 acaccagatc actcttctct ctaccacag gcttgctatg agcaagagac acaacctctc 120  
 ctctctgtg ttccagcttc ttctctgtt ctccccccc cttaagttct attcctgggg 180  
 atagagacac caatacccat aacctctctc ctaagcctcc ttataaccca gggcgacag 240  
 cacagaactc tgacaactgg taaggccaat gaactgggag ctccagctg gctgtgcctg 300  
 a 301

<210> 267  
 <211> 301  
 <212> DNA  
 <213> Homo sapien

<400> 267  
 aaagagcaca ggccagctca gcctgccctg gccatctaga ctccagcctg ctccatgggg 60  
 gttctcagtg ctgagtcctat ccaggaaaag ctccctaga cttctctgag ctgaatcttc 120  
 atcttcacag gcagcttctg agagcctgat attcctagcc ttgatggctt ggagtaaagc 180  
 ctctctctga ttctctctct tcttttctt caagttggct ttcttcacat cctctctgtc 240  
 aattcgtctc agcttgtctg ctttagccct catttcaga agcttctct ctttggcctc 300  
 t 301

<210> 268  
 <211> 301  
 <212> DNA  
 <213> Homo sapien

<400> 268  
 aatgtctcac tcaactactt cccagcctac cgtggcctaa ttctgggagt ttctttctta 60  
 gatcttggga gagctgggtc ttctaaggag aaggaggaag gacagatgta actttggatc 120  
 tcgaagagga agtctaattg aagtaattag tcaacggtcc ttgttttagac tcttgggaata 180  
 tgctgggttg ctccagtggc ctttttggag aaagcaagta ttattcttaa ggagtaacca 240  
 ctccccattg ttctacttct taccatcatc aattgtatat tatgtattct ttggagaact 300  
 a 301

<210> 269  
 <211> 301  
 <212> DNA  
 <213> Homo sapien

<400> 269  
 taacaatata cactagctat ctttttaact gtccatcatt agcaccaatg aagattcaat 60  
 aaaattacct ttattcacac atctcaaaac aattctgcaa attcttagtg aagtttaact 120  
 atagtcacag accttaataa ttcacattgt tttctatgtc tactgaaaat aagttcacta 180  
 cttttctgga tattctttac aaaatcttat taaaattcct ggtattatca cccccaatta 240  
 tacagtagca caaccacctt atgtagtttt tacatgatag ctctgtagaa gtttcacatc 300  
 t 301

<210> 270  
 <211> 301  
 <212> DNA  
 <213> Homo sapien

<400> 270  
 cattgaagag cttttgagaa acatcagaac acaagtgttt ataaaattaa ttaagcctta 60  
 cacaagaata catattcctt ttattttctaa ggaggttaaac atagatgtag ctgatgtgga 120  
 gagcttgctc gtgcagtgc tattggataa cactattcat ggccgaattg atcaagtcaa 180  
 ccaactcctt gaactggatc atcagaagaa ggggtggtgca cgatatactg cactagataa 240  
 tggaccaacc aactaaattc tctcaccagg ctgtatcagt aaactggctt aacagaaaac 300  
 a 301

<210> 271  
 <211> 301  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(301)  
 <223> n = A,T,C or G

<400> 271  
 aaaaggttct cataagatla acaattttaa taaatatttg atagaacatt ctttctcatt 60  
 tttatagctc atcttttaggg ttgatattca gttcatgttt cctttgctgt tcttgatcca 120  
 gaattgcaat cacttcatca gctgtattc gctccaattc tctataaagt ggggtccaagg 180  
 tgaaccacag agccacagca cactcttttc ccttggtgac tgccttcacc ccatganggt 240  
 tctctcctcc agatganaac tgatcatgag cccacatttt ggggtttata gaagcagtca 300  
 c 301

<210> 272  
 <211> 301  
 <212> DNA  
 <213> Homo sapien

<400> 272  
 taaattgcta agccacagat aacaccaatc aaatggaaca aatcactgtc ttcaaagtgc 60  
 ttatcagaaa accaaatgag cctggaatct tcataatacc taaacatgcc gtatttagga 120  
 tccaataatt cctcatgat gagcaagaaa aattctttgc gcacccctcc tgcattccca 180  
 gcatcttctc caacaaatat aaccttgagt ggcttcttgt aatctatgtt ctttgttttc 240  
 ctaaggactt ccattgcac tctacaata ttttctctac gcaccactag aattaagcag 300  
 g 301

<210> 273  
 <211> 301  
 <212> DNA  
 <213> Homo sapien

<220>



<221> misc\_feature  
 <222> (1)...(301)  
 <223> n = A,T,C or G

<400> 273  
 acatgtgtgt atgtgtatct ttgggaaaaan aanaagacat cttgtttayt atttttttgg 60  
 agagangctg ggacatggat aatcacwtaa tttgctayta tyactttaat ctgactygaa 120  
 gaaccgtcta aaaataaaat ttaccatgct diatattcct tatagtatgc ttatttcacc 180  
 ttytttctgt ccagagagag tatcagtgac ananatttma ggggtgaamac atgmattggg 240  
 gggactntny tttacngagm accctgcccg sgcgccctcg makcngantt ccgcsananc 300  
 t 301

<210> 274  
 <211> 301  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(301)  
 <223> n = A,T,C or G

<400> 274  
 cttatatact ctttctcaga ggcaaaagag gagatgggta atgtagacaa ttctttgagg 60  
 aacagtaaat gattattaga gagaangaat ggaccaagga gacagaaatt aacttgtaaa 120  
 tgattctctt tggaatctga atgagatcaa gaggccagct ttagcttggt gaaaagtcca 180  
 tctaggtatg gttgcattct cgtcttcttt tctgcagtag ataatgaggt aaccgaaggc 240  
 aattgtgctt cttttgataa gaagctttct tggtcataac aggaaattcc aganaaaagtc 300  
 c 301

<210> 275  
 <211> 301  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(301)  
 <223> n = A,T,C or G

<400> 275  
 tcggtgtcag cagcacgtgg cattgaacat tgcaatgtgg agcccaaacc acagaaaatg 60  
 qggtgaaaatt ggccaacttt ctattaactt atgttggcaa ttttgccacc aacagtaagc 120  
 tggcccttct aataaaagaa aattgaaagg tttctcacta aacggaatta agtagtggag 180  
 tcaagagact ccagggctc agcgtacctg cccggggcgc cgctcgaagc cgaattctgc 240  
 agatatccat cacactggcg gncgctcgan catgcactta gaaggnccaa ttgcgcctat 300  
 a 301

<210> 276  
 <211> 301  
 <212> DNA  
 <213> Homo sapien

<400> 276  
 tgtacacata ctcaataaat aaatgactgc attgtgggtat tattactata ctgattatat 60  
 ttatcatgtg actttctaatt agaaaatgta tccaaaagca aaacagcaga tatacaaaat 120  
 taaagagaca gaagatagac attaacagat aaggcaactt atacattgag aatccaaatc 180  
 caatacattt aaacatttgg gaaatgaggg ggacaaatgg aagccagatc aaatttctgt 240

aaaactattc agtatgtttc ccttgcttca tgtctgagaa ggctctcctt caatggggat 300  
g 301

<210> 277  
<211> 301  
<212> DNA  
<213> Homo sapien

<220>  
<221> misc\_feature  
<222> (1)...(301)  
<223> n = A,T,C or G

<400> 277  
tttgttgatg tcagtatttt attacttgcg ttatgagtgc tcacctggga aattctaaag 60  
atacagagga cttggaggaa gcagagcaac tgaatttaat ttaaaagaag gaaaacattg 120  
gaatcatggc actcctgata ctttcccaaa tcaacactct caatgccccca cctcgtcct 180  
caccatagtg gggagactaa agtggccacg gatttgccct angtggtcag tgcgtttctga 240  
gttcnctgtc gattacatct gaccagtctc ctttttccga agtcnctccg ttcaatcttg 300  
c 301

<210> 278  
<211> 301  
<212> DNA  
<213> Homo sapien

<220>  
<221> misc\_feature  
<222> (1)...(301)  
<223> n = A,T,C or G

<400> 278  
taccactaca ctccagcctg ggcaacagag caagacctgt ctcaaagcat aaaatggaat 60  
aacatatcaa atgaaacagg gaaaatgaag ctgacaattt atggaagcca gggcttgatc 120  
cagtctctac tgttattatg cattacctgg gaatttatat aagcccttaa taataatgcc 180  
aatgaacatc tcatgtgtgc tcacaatggt ctggcactat tataagtgtc tcacaggttt 240  
tatgtgttct tcgtaacttt atggantagg tactcggccg cgaacacgct aagccgaatt 300  
c 301

<210> 279  
<211> 301  
<212> DNA  
<213> Homo sapien

<220>  
<221> misc\_feature  
<222> (1)...(301)  
<223> n = A,T,C or G

<400> 279  
aaagcaggaa tgacaaagct tgcttttctg gtatgttcta ggtgtattgt gacttttact 60  
gttatattaa ttgccaatat aagtaaatat agattatata tgtatagtgt ttcacaaagc 120  
ttagaccttt acctccagc caccacacag tgcttgatat ttcagagtca gtcattggtt 180  
atacatgtgt agttccaaag cacataagct agaanaanaa atatttctag ggagcactac 240  
catctgtttt cacatgaaat gccacacaca tagaactcca acatcaattt cattgcacag 300  
a 301

<210> 280

<211> 301  
 <212> DNA  
 <213> Homo sapien

<400> 280  
 ggtactggag ttttctctcc ctgtgaaaac gtaactactg ttgggagtga attgaggatg 60  
 taqaaagggtg gtggaaccaa attgtggtca atggaaatag gagaatatgg ttctcactct 120  
 agagaaaaaa acctaagatt agcccaggta gttgcctgta acctcagttt ttctgcctgg 180  
 gttagatata gtttaggggtt ggggttagat taagatctaa attacatcag gacaaagaga 240  
 cagactatta actccacagt taattaagga ggtatgttcc atgtttattt gttaaagcag 300  
 r 301

<210> 281  
 <211> 301  
 <212> DNA  
 <213> Homo sapien

<400> 281  
 aggtacaaga aggggaatgg gaaagagctg ctgctgtggc attgttcaac ttggatatc 60  
 gccgagcaat ccaaactcctg aatgaagggt catcttctga aaaaggagat ctgaatctca 120  
 atgtggtagc aatggcttta tcgggttata cggatgagaa gaactccctt tggagagaaa 180  
 tgtgtagcac actgcgatta cagctaaata acccgtatct gtgtgtcatg ttgtcatttc 240  
 tgacaagtga aacaggatct tacgatggag ttttgtatga aaacaaagt gacgtacctc 300  
 g 301

<210> 282  
 <211> 301  
 <212> DNA  
 <213> Homo sapien

<400> 282  
 caqutactac agaattaaaa tactgacaag caagtagttt cttggcgtgc acgaattgca 60  
 tccagaaccc aaaaattaag aaattcaaaa agacattttg tgggcacctg ctagcacaga 120  
 aggcgagaag caaagcccag gcagaaccat gctaacccta cagctcagcc tgcacagaag 180  
 cgcagaagca aagcccaggc agaaccatgc taaccttaca gctcagcctg cacagaagcg 240  
 cagaagcaaa gcccaggcag aacatgctaa ccttacagct cagcctgcac agaagcacag 300  
 a 301

<210> 283  
 <211> 301  
 <212> DNA  
 <213> Homo sapien

<400> 283  
 atctgtatac ggcagacaaa ctttatarag tgtagagagg tgagcgaaag gatgcaaaag 60  
 cactttgagg gctttataat aatatgctgc ttgaaaaaaa aaatgtgtag ttgatactca 120  
 gtgcactctc agacatagta aggggttgct ctgaccaatc aggtgatcat ttttctatc 180  
 acttcccagg ttttatgcaa aaattttgtt aaattctata atggtgatat gcacttttta 240  
 ggaaacatat acatttttaa aaatctatct tatgtaagaa ctgacagacg aatttgcttt 300  
 g 301

<210> 284  
 <211> 301  
 <212> DNA  
 <213> Homo sapien

<400> 284  
 caggtacaaa acgctattaa gtggcttaga atttgaacat ttgtggtctt tatttacttt 60

```

gcttcgtgtg tgggcaaagc aacatcttcc ctaaataatat attaccaaga aaagcaagaa 120
gcagattagg tttttgacaa aacaaaacagg ccaaaagggg gctgacctgg agcagagcat 180
ggtgagaggc aaggcatgag agggcaagtt tgttgtggac agatctgtgc ctactttatt 240
actggagtaa aagaaaacaa agttcattga tgtcgaagga tatatacagt gttagaaatt 300
a 301

```

```

<210> 285
<211> 301
<212> DNA
<213> Homo sapien

```

```

<220>
<221> misc_feature
<222> (1)...(301)
<223> n = A,T,C or G

```

```

<400> 285
acatcaccat gatcggatcc cccacccatt atacgttgta tgtttacata aatactcttc 60
aatgatcatt agtgttttaa aaaaaatact gaaaactcct tctgcatccc aatctctaac 120
caggaaagca aatgctatct acagacctgc aagccctccc tcaaacnaaa ctatttctgg 180
attaaatatg tctgacttct tttgaggtca cagcactagg caaatgctat ttacgatctg 240
caaaagctgt ttgaagagtc aaagcccca tgtgaacacg atttctggac cctgtaacag 300
t 301

```

```

<210> 286
<211> 301
<212> DNA
<213> Homo sapien

```

```

<400> 286
taccactgca ttccagcctg ggtgacagag tgagactcog tctccaaaaa aaactttgct 60
tgtatattat ttttgacctt cagtggatca ttctagtagg aaaggacagt aagatttttt 120
atcaaaatgt gtcatgccag taagagatgt tatattcttt tctcatttct tccccacca 180
aaaataagct accatatagc ttataagtct caaatttttg ctttttacta aaatgtgatt 240
gtttctgttc attgtgtatg cttcatcacc tatattaggc aaattccatt tttcccttg 300
t 301

```

```

<210> 287
<211> 301
<212> DNA
<213> Homo sapien

```

```

<400> 287
tacagatctg ggaactaaat attaaaaatg agtgtggctg gatatatgga gaatgttggg 60
cccagaagga acgtagagat cagatattac aacagctttg ttttgagggt tagaaatatg 120
aaatgatttg gttatgaacg cacagtttag gcagcagggc cagaatcctg accctctgcc 180
ccgtggttat ctcctcccca gcttggtgc ctcagtgtat cacagtattc cattttgttt 240
gttgcattgc ttgtgaagcc atcaagattt tctcgtctgt tttcctctca ttggtaatgc 300
t 301

```

```

<210> 288
<211> 301
<212> DNA
<213> Homo sapien

```

```

<400> 288
gtacacctaa ctgcaaggac agctgaggaa tgtaatgggc agccgctttt aaagaagtag 60
agtcaatagg aagacaaatt ccagttccag ctcagtctgg gtatctgcaa agctgcaaaa 120

```

```

gatactttaa gacaatttca agagaatatt tccttaaagt tggcaatttg gagatcatac 180
aaaagcatct gcttttgtga ttttaatttag ctcatctggc cactggaaga atccaaacag 240
tctgacttaa ttttgatga atgcatgatg gaaattcaat aatttagaaa gttaaaaaaaa 300
a 301

```

```

<210> 289
<211> 301
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(301)
<223> n = A,T,C or G

```

```

<400> 289
ggtacactgt ttccatgtta tgtttctaca cattgctacc tcagtgtccc tggaaactta 60
gcttttcatg tctccaagta gtccaccttc atttaactct ttgaaactgt atcatctttg 120
ccaagtaaga gtggtggcct atttcagctg ctttgacaaa atgactggct cctgacttaa 180
cgttctataa atgaatgtgc tgaagcaaag tgcccatggt ggcggcgaan aagagaaaaga 240
tgtgttttgt tttggactct ctgtgggtccc ttccaatgct gtgggtttcc aaccagnnga 300
a 301

```

```

<210> 290
<211> 301
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(301)
<223> n = A,T,C or G

```

```

<400> 290
acactgagct cttcttgata aatatacaga atgcttggca tatacaagat tctatactac 60
tgactgatct gttcatttct ctccacagtc ttacccccaa aagcttttcc accctaagtg 120
ttctgacctc cttttctaat cacagtaggg atagaggcag anccacctac aatgaacatg 180
gagttctatc aagaggcaga aacagcacag aatcccagtt ttaccattcg ctagcagtgc 240
tgcttgaac aaaaacattt ctccatgtct cattttcttc atgcctcaag taacagtga 300
a 301

```

```

<210> 291
<211> 301
<212> DNA
<213> Homo sapien

```

```

<400> 291
caggtaacaa tttcttctat cctagaaaca tttcatttta tgttggtgaa acataacaac 60
tatatcagct agattttttt tctatgcttt acctgctatg gaaaatttga cacattctgc 120
tttactcttt tgtttatagg tgaatcacia aatgtatttt tatgtattct gtagttcaat 180
agccatggct gtttacttca ttttaattat ttagcataaa gacattatga aaaggcctaa 240
acatgagctt cacttcccca ctaactaatt agcatctggt atttcttaac cgtaatgct 300
a 301

```

```

<210> 292
<211> 301
<212> DNA
<213> Homo sapien

```

<220>  
 <221> misc\_feature  
 <222> (1)...(301)  
 <223> n = A,T,C or G

<400> 292  
 accttttagt agtaatgtct aataataaat aagaaatcaa ttttataagg tccatatagc 60  
 tgtatttaaat aatttttaag tttaaaagat aaaataccat catttttaaat gttggtattc 120  
 aaaaccaaag natataaccg aaaggaaaaa cagatgagac ataaaatgat ttgcnagatg 180  
 ggaaatatag tasttyatga atgttnatta aattccagtt ataatagtgg ctacacactc 240  
 tcactacaca cacagacccc acagtcctat atgccacaaa cacatttcca taacttgaaa 300  
 a 301

<210> 293  
 <211> 301  
 <212> DNA  
 <213> Homo sapien

<400> 293  
 ggtaccaagt gctgggtgcc gctgttacc tgttctcact gaaaagtctg gctaattgctc 60  
 ttgtgtagtc acttctgatt ctgacaatca atcaatcaat ggctagagc actgactgtt 120  
 aacacaaacg tctactagcaa agtagcaaca gctttaagtc taaatacaaa gctgttctgt 180  
 gtgagaattt tttaaaaggc tacttgtata ataacccttg tcatttttaa tgtacctcg 240  
 ccgcgaccac gctaagccga attctgcaga tatccatcac actggcggcc gctcgagcat 300  
 g 301

<210> 294  
 <211> 301  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(301)  
 <223> n = A,T,C or G

<400> 294  
 tgaccataa caatatacac tagctatctt ttttaactgtc catcattagc accaatgaag 60  
 attcaataaa attaccttta ttcacacatc tcaaaacaat totgcaaatt cttagtgaag 120  
 ttttaactata gtcacaganc ttaaatattc acattgtttt ctatgtctac tgaaaataag 180  
 ttcactactt ttctgggata ttctttacaa aatcttatta aaattcctgg tattatcacc 240  
 cccaattata cagtagcaca accaccttat gtagtittta catgatagct ctgtagaggt 300  
 t 301

<210> 295  
 <211> 305  
 <212> DNA  
 <213> Homo sapien

<400> 295  
 gtactctttc tctcccctcc tctgaattta attctttcaa cttgcaattt gcaaggatta 60  
 cacatttcac tgtgatgtat atttgtttgc aaaaaaaaaa gtgtctttgt ttaaaattac 120  
 ttggtttgtg aatccatctt gctttttccc cattggaact agtcattaac ccatctctga 180  
 actggtagaa aaacrtctga agagctagtc tatcagcatc tgacagggtga attggatggt 240  
 tctcagaacc atttcaccca gacagcctgt ttctatcctg ttttaataaat tagtttggtt 300  
 tctct 305

<210> 296  
 <211> 301  
 <212> DNA  
 <213> Homo sapien

<400> 296  
 aggtactatg ggaagctgct aaaataatat ttgatagtaa aagtatgtaa tgtgctatct 60  
 cacctagtag taaactaaaa ataaactgaa actttatgga atctgaagtt attttccctg 120  
 attaaataga attaataaac caatatgagg aaacatgaaa ccatgcaatc tactatcaac 180  
 tttgaaaaag tgattgaacg aaccacttag ctttcagatg atgaacactg ataagtcatt 240  
 tgtcattact ataaatttta aaatctgtta ataagatggc ctatagggag gaaaaagggg 300  
 c 301

<210> 297  
 <211> 300  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(300)  
 <223> n = A,T,C or G

<400> 297  
 actgagtttt aactggacgc caagcaggca aggetggaag gttttgctct ctttgctcta 60  
 aaggttttga aaaccttgaa ggagaatcat ttgacaaga agtacttaag agtctagaga 120  
 acaaagangt gaaccagctg aaagctctcg ggggaanctt acatgtgttg ttaggcctgt 180  
 tccatcattg ggagtgcact ggccatccct caaaattttg ctgggctggc ctgagtggtc 240  
 accgcacctc ggccgcgacc acgctaagcc gaattctgca gatatccatc acactggcgg 300

<210> 298  
 <211> 301  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(301)  
 <223> n = A,T,C or G

<400> 298  
 tatggggttt gtcacccaaa agctgatgct gagaaaggcc tccctggggc cctcccgcg 60  
 ggcctctgag agacctgggtg ttccagtgtt tctggaaatg ggtcccagtg ccgcccgtg 120  
 tgaagctctc agatcaatca cgggaagggc ctggcggttg tggccacctg gaaccaccct 180  
 gtctgtctg tttacatttc actaycagg tttctctggg cattacnatt tgttccccta 240  
 caacagtgac ctgtgcattc tgctgtggcc tgctgtgtct gcaggtggct ctccagcgag 300  
 t 301

<210> 299  
 <211> 301  
 <212> DNA  
 <213> Homo sapien

<400> 299  
 gttttgagac ggagtttccac tcttggttgc cagactggac tgcaatggca gggctctctgc 60  
 tcaactgcacc ctctgcctcc cagggttcgag caattctcct gcctcagcct ccaggttagc 120  
 tgggattgca ggctcacgcc accataccca gctaattttt ttgtattttt agtagagacg 180  
 gagtttccgc atgttgggca gctgggtctc aactcctgac ctcaagcgac ctgcctgctc 240

cggcctccca aagtgctgga attataggca tgagtcaaca cgcccagcct aaagatattt 300  
t 301

<210> 300  
<211> 301  
<212> DNA  
<213> Homo sapien

<400> 300  
attcagtttt atttgctgcc ccagtatctg taaccaggag tgccacaaaa tcttgccaga 60  
tatgtcccac acccactggg aaaggctccc acctggctac ttctctctatc agctgggtca 120  
gctgcattcc acaaggttct cagcctaattg agtttcaacta cctgccagtc tcaaaactta 180  
gtaaagcaag accatgacat tccccacgg aaatcagagt ttgccccacc gtcttggttac 240  
tataaagcct gcctctaaca gtccttgctt cttcacacca atcccgagcg catcccccat 300  
g 301

<210> 301  
<211> 301  
<212> DNA  
<213> Homo sapien

<400> 301  
ttaaatTTTT gagaggataa aaaggacaaa taatctagaa atgtgtcttc ttcagtctgc 60  
agaggacccc aggtctccaa gcaaccacat ggtcaagggc atgaataatt aaaagttggt 120  
gggaactcac aaagaccctc agagctgaga caccacacac agtgggagct cacaaagacc 180  
ctcagagctg agacaccac aacagtggga gctcaciaag accctcagag ctgagacacc 240  
cacaacagca cctcggtcag ctgccacatg tgtgaataag gatgcaatgt ccagaagtgt 300  
t 301

<210> 302  
<211> 301  
<212> DNA  
<213> Homo sapien

<400> 302  
aggtacacat ttagcttgtg gtaaatgact cacaaaactg atttttaaatt caagttaatg 60  
tgaattttga aaattactac ttaatcctaa ttcacaataa caatggcatt aaggtttgac 120  
ttgagttggt tcttagtatt atttatggta aataggtctt taccacttgc aaataactgg 180  
ccacatcatt aatgactgac ttcccagtaa ggctctctaa ggggtaagta ggaggatcca 240  
caggatttga gatgctaagg ccccagagat cgtttgatcc aaccctctta ttttcagagg 300  
g 301

<210> 303  
<211> 301  
<212> DNA  
<213> Homo sapien

<400> 303  
aggtaccaac tgtggaaata ggtagaggat cattttttct ttccatatca actaagttgt 60  
atattgtttt ttgacagttt aacacatctt cttctgtcag agattctttc acaatagcac 120  
tggctaattg aactaccgct tgcattgtta aaatgggtgt ttgtgaaatg atcataggcc 180  
agtaacgggt atgtttttct aactgatctt ttgctcgttc caaagggacc tcaagacttc 240  
catcgatttt atatctgggg tctagaaaag gagttaatct gttttccctc ataaattcac 300  
c 301

<210> 304  
<211> 301  
<212> DNA



<213> Homo sapien

<400> 304

acatggatgt	tattttgcag	actgtcaacc	tgaatttcta	tttgcttgac	attgcctaata	60
tattagtttc	agtttcagct	tacccacttt	ttgtctgcaa	catgcaraas	agacagtgcc	120
cttttttagtg	tatcatatca	ggaatcatct	cacattgggt	tgtgccatta	ctgggtgcagt	180
gaatttcagc	cacttgggta	aggtggagtt	ggccatatgt	ctccactgca	aaattactga	240
ttttcccttt	gtaattaata	agtgtgtgtg	tgaagattct	ttgagatgag	gtatataatc	300
a						301

<210> 305

<211> 301

<212> DNA

<213> Homo sapien

<220>

<221> misc\_feature

<222> (1)...(301)

<223> n = A,T,C or G

<400> 305

gaagtacagc	gtgggtcaag	taacaagaag	aaaaaaatgt	gagtggcatc	ctgggatgag	60
cagggggaca	gacctggaca	gacacgttgt	catttgctgc	tgtgggtagg	aaaatgggag	120
taaaggagga	gaaacagata	caaaatctcc	aactcagtat	taaggatttc	tcatgcctag	180
aatatttgta	gaaacaagaa	tacattcata	tggcaataaa	ctaaccatgg	tggacaacaaa	240
ttctgggatt	taagttggat	accaangaaa	ttgtattaaa	agagctgttc	atggaataag	300
a						301

<210> 306

<211> 8

<212> PRT

<213> Homo sapien

<400> 306

Val	Leu	Gly	Trp	Val	Ala	Glu	Leu
1				5			

<210> 307

<211> 637

<212> DNA

<213> Homo sapien

<400> 307

acaggggratg	aagggaaaag	gagaggatga	ggaagccccc	ctggggattt	ggtttggtcc	60
ttgtgatcag	gtgggtctatg	gggcttatcc	ctacaaaagaa	gaatccagaa	ataggggcac	120
attgaggaat	gatacttgag	cccaaagagc	attcaatcat	tgtttttattt	gccttmtttt	180
cacaccattg	gtgagggagg	gattaccacc	ctgggggttat	gaagatgggt	gaacacocca	240
cacatagcac	cggagatatg	agatcaacag	tttcttagcc	atagagattc	acagcccaga	300
gcaggaggac	gcttgacac	catgcaggat	gacatggggg	atgcgctcgg	gattgggtgtg	360
aagaagcaag	gactgttaga	ggcaggcttt	atagtaacaa	gacgggtggg	caaactctga	420
ttlccgtggg	ggaatgtcat	ggtcttgctt	tactaagttt	tgagactggc	aggtagtga	480
actcattagg	ctgagaacct	tgtggaatgc	acttgaccca	scgatagag	gaagtagcca	540
qgtgggagcc	tttcccagtg	ggtgtgggac	atatctggca	agattttgtg	gcactcctgg	600
ttacagatac	tggggcagca	aataaaaactg	aatcttg			637

<210> 308

<211> 647

<212> DNA

<213> Homo sapien

<220>

<221> misc\_feature

<222> (1) ... (647)

<223> n = A,T,C or G

<400> 308

acgattttca	ttatcatgta	aatcgggtca	ctcaaggggc	caaccacagc	tgggagccac	60
tgctcagggg	aaggttcata	tgggactttc	tactgcccaa	ggttctatac	aggatataaa	120
ggngcctcac	agtatagatc	tggtagcaaa	gaagaagaaa	caaacactga	tctctttctg	180
ccacccctct	gaccctttgg	aactcctctg	accctttaga	acaagcctac	ctaatatctg	240
ctagagaaaa	gaccaacaac	ggcctcaaag	gatctcttac	catgaaggtc	tcagctaatt	300
cttgggctaag	atgtgggttc	cacattaggt	tctgaatatg	gggggaaggg	tcaatttgct	360
catttttgtgt	gtggataaag	tcaggatgcc	caggggccag	agcagggggc	tgcttgcttt	420
gggaacaatg	gctgagcata	taaccatagg	ttatggggaa	caaaacaaca	tcaaagtcac	480
tgtatcaatt	gccatgaaga	cttgagggac	ctgaatctac	cgattcatct	taaggcagca	540
ggaccagttt	gagtggcaac	aatgcagcag	cagaatcaat	ggaaacaaca	gaatgattgc	600
aatgtccttt	ttttctctct	gcttctgact	tgataaaagg	ggaccgt		647

<210> 309

<211> 460

<212> DNA

<213> Homo sapien

<400> 309

actttatagt	ttaggctgga	cattggaaaa	aaaaaaaaagc	cagaacaaca	tgtgatagat	60
aatatgattg	gctgcacact	tccagactga	tgaatgatga	acgtgatgga	ctattgtatg	120
gagcacatct	tcagcaagag	ggggaaatac	tcatcatttt	tggccagcag	ttgtttgatc	180
accaaaccatc	atgccagaat	actcagcaaa	ccttctttagc	tcttgagaag	tcaaagtcog	240
ggggaattta	ttcctggcaa	ttttaattgg	actccttatg	tgagagcagc	ggctaccacg	300
ctggggtggt	ggagcgaacc	cgtcactagt	ggacatgcag	tggcagagct	cctggtaacc	360
acctagagga	atacacaggc	acatgtgtga	tgccaagcgt	gacacctgta	gcactcaaat	420
ttgtcttggt	tttgtctttc	ggtgtgtaag	attcttaagt			460

<210> 310

<211> 539

<212> DNA

<213> Homo sapien

<400> 310

acgggactta	tcaaataaag	ataggaaaag	aagaaaactc	aaatattata	ggcagaaatg	60
ctaaaggttt	taaaatatgt	caggattgga	agaaggcatg	gataaagaac	aaagttcagt	120
taggaaagag	aaacacagaa	ggaagagaca	caataaaagt	cattatgtat	tctgtgagaa	180
gtcagacagt	aagattttgtg	ggaaatgggt	tggtttgttg	tatggtatgt	attttagcaa	240
taatctttat	ggcagagaaa	gctaaaatcc	tttagcttgc	gtgaatgatc	acttgctgaa	300
ttcctcaagg	taggcatgat	gaaggagggt	ttagaggaga	cacagacaca	atgaactgac	360
ctagatagaa	agccttagta	tactcagcta	ggaatagtga	ttctgagggc	acactgtgac	420
atgattatgt	cattacatgt	atggtagtga	tggggatgat	aggaaggaag	aacttatggc	480
atattttcac	ccccacaaa	gtcagttaaa	tattgggaca	ctaaccatcc	aggtcaaga	539

<210> 311

<211> 526

<212> DNA

<213> Homo sapien

<220>

<221> misc\_feature

&lt;222&gt; (1)...(526)

&lt;223&gt; n = A,T,C or G

&lt;400&gt; 311

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ttttgacgtt	ttctctaaac	tactaaagag	gcattaatga	tccataaatt	atattatcta	120
catttacagc	atttaaaatg	tgttcagcat	gaaatattag	ctacagggga	agctaaataa	180
attaaacatg	gaataaagat	ttgtccttaa	atataatcta	caagaagact	ttgatatttg	240
tttttcacaa	gtgaagcatt	cttataaagt	gtcataacct	ttttggggaa	actatgggaa	300
aaaatgggga	aactctgaag	ggttttaagt	atcttacctg	aagctacaga	ctccataacc	360
tctcttttaca	gggagctcct	gcagccccta	cagaaatgag	tggttgagat	tcttgattgc	420
acagcaagag	cttctcatct	aaaccctttc	ccttttttagt	atctgtgtat	caagtataaa	480
agttctataa	actgtagtnt	acttatttta	atccccaag	cacagt		526

&lt;210&gt; 312

&lt;211&gt; 500

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; (1)...(500)

&lt;223&gt; n = A,T,C or G

&lt;400&gt; 312

cctctctctc	cccaccccct	gactctagag	aactgggttt	tctcccagta	ctccagcaat	60
tcattttctga	aagcagttga	gccactttat	tccaaagtac	actgcagatg	ttcaaactct	120
ccattttctct	ttcccttcca	cctgccagtt	ttgctgactc	tcaacttgtc	atgagtgtaa	180
gcattaagga	cattatgctt	cttcgattct	gaagacaggc	cctgctcatg	gatgactctg	240
gcttcttagg	aaaatatatt	tcttccaaaa	tcagtaggaa	atctaaactt	atccctctct	300
tgcagatgtc	tagcagcttc	agacatttgg	ttaagaacct	atgggaaaaa	aaaaaatcct	360
tgctaattgt	gtttcctttg	ttaaccanga	ttcttatttg	netggatatag	aatatcagct	420
ctgaacgtgt	ggtaaagatt	tttgtgtttg	aatataggag	aatcagttt	gctgaaaagt	480
tagtcttaat	tatctatttg					500

&lt;210&gt; 313

&lt;211&gt; 718

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; (1)...(718)

&lt;223&gt; n = A,T,C or G

&lt;400&gt; 313

ggagatttgt	gtggtttgca	gccgagggag	accaggaaga	tctgcatggt	gggaaggacc	60
tgatgatata	gaggtgagaa	ataagaaaag	ctgctgactt	taccatctga	ggccacacat	120
ctgctgaaat	ggagataatt	aacatcacta	gaaacagcaa	gatgacaata	taatgtctaa	180
gtagtgacat	gtttttgcac	atttccagcc	cttttaataa	tccacacaca	caggaagcac	240
aaaaggaagc	acagagatcc	ctgggagaaa	tgcccggccg	ccatcttggg	tcatcgatga	300
gcctcgccct	gtgcctgntc	ccgcttggtg	gggaaggaca	ttagaaaatg	aattgatgtg	360
ttccttaaa	gatggcagga	aaacagatcc	tggttggtg	atttatttga	acgggattac	420
agatttgaaa	tgaagtcaca	aagtgaagcat	taccaatgag	aggaaaacag	acgagaaaat	480
cttgatgggt	cacaagacat	gcaacaaa	aaatggaata	ctgtgatgac	acgagcagcc	540
aactggggag	gagataccac	ggggcagag	tcaggattct	ggccctgctg	cctaactgtg	600
cgttatacca	atcattttcta	tttctaccct	caaacaagct	gtngaataatc	tgacttacgg	660
ttcttntggc	ccacattttc	atnatccacc	ccntentttt	aannttantic	caaantgt	718

<210> 314  
 <211> 358  
 <212> DNA  
 <213> Homo sapien

<400> 314  
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 caacatgtgt agatctcttg tcttattctt ttgtctataa tactgtattg tgtagtccaa 180  
 gctctcggtg gtccagccac tgtgaaacat gctcccttta gattaacctc gtggacgctc 240  
 ttgttggtatt gctgaactgt agtgccctgt attttgcttc tgtctgtgaa ttctgttget 300  
 tctggggcat ttccttgtga tgcagaggac caccacacag atgacagcaa tctgaatt 358

<210> 315  
 <211> 341  
 <212> DNA  
 <213> Homo sapien

<400> 315  
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 gacccccatt ctgaagatgt ctggaacctc taccagcagg atgatgatag cccaatgac 180  
 agtcaccagc tccccgacca gccggatata gtccttaggg gtcattgtagg ctctctgaag 240  
 tagcttctgc tgtaagaggg tgttgctccc ggggctcgtg cgggttattgg tcttgggctt 300  
 gagggggcgg tagatgcagc acatggtgaa gcagatgatg t 341

<210> 316  
 <211> 151  
 <212> DNA  
 <213> Homo sapien

<400> 316  
 agactgggca agactcttac gccccacact gcaatttggg cttgttgccg tatccattta 60  
 tgtgggcctt tctcgagttt ctgattataa acaccactgg agcgatgtgt tgactggact 120  
 cattcagga gctctgggtg caatattagt t 151

<210> 317  
 <211> 151  
 <212> DNA  
 <213> Homo sapien

<400> 317  
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 atcttcattt atctctggcc ttaaccctgg ctccctgaggg tgcggccagc agatcccagg 120  
 ccagggtct gttcttgcca cacctgcttg a 151

<210> 318  
 <211> 151  
 <212> DNA  
 <213> Homo sapien

<400> 318  
 actggtgagg ggcgtgttt agttggctgt ttccagaggg gtctttcgga gggacctcct 60  
 gctgcaggct ggagtgtctt tattcctggc gggagaccgc acattccact gctgaggctg 120  
 tgggggcggg ttatcaggca gtgataaaca t 151

<210> 319

<211> 151  
 <212> DNA  
 <213> Homo sapien

<400> 319  
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 caatacatagt actaggtatt aatagatatg taaagaaaga aatcacacca ttaataatgg 120  
 taagattggg tttatgtgat tttagtgggt a 151

<210> 320  
 <211> 150  
 <212> DNA  
 <213> Homo sapien

<400> 320  
 aactagtggg tccactagtc cagtgtgggt gaattccatt gtgttggggg tctagatcgc 60  
 gagcggtgc cctttttttt ttttttttg ggggggaatt tttttttttt aatagttatt 120  
 gagtgttcta cagcttacag taaataccat 150

<210> 321  
 <211> 151  
 <212> DNA  
 <213> Homo sapien

<400> 321  
 agcaactttg tttttcatcc aggttatatt aggcttagga tttcctctca cactgcagtt 60  
 taggggtggc ttgtaaccag ctatggcata ggtgttaacc aaaggctgag taaacatggg 120  
 tgcctctgag aatcaaagt cttcatacac t 151

<210> 322  
 <211> 151  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(151)  
 <223> n = A,T,C or G

<400> 322  
 atccagcacc ttctcctggt tcttgccctc ctttttcttc ttcttasatt ctgcttgagg 60  
 tttgggcttg gtcagtttgc cacagggctt ggagatgggt acagtcttct ggcattcggc 120  
 attgtgcagg gctcgttca nacttccagt t 151

<210> 323  
 <211> 151  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(151)  
 <223> n = A,T,C or G

<400> 323  
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 nagactcant tactaccag tttgtgggtt twtgggagaa atgtaactgg acagttagct 120  
 gttcaatyaa aaagacactt anccatgtg g 151

<210> 324  
 <211> 461  
 <212> DNA  
 <213> Homo sapien  
  
 <220>  
 <221> misc\_feature  
 <222> (1)...(461)  
 <223> n = A,T,C or G

<400> 324  
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 agaagtgttc agctaaagga atccagggtg ttggttgac tgtaataacc ttgatgaaa 120  
 agagttacta cgaatcccat cttggttcca gctatatcac tgacagcatg gtagaagact 180  
 gcgaacctca cttctagact ttacagggtg gacgaaacgg gttcagaaac tgccaggggc 240  
 ctcatacagg gatatacaaa taccctttgt gctaccagg ccctggggaa tcagggtgact 300  
 cacacaaatg caatagttgg tcaactgcatt tttacctgaa ccaaagctaa acccggtgtt 360  
 gccaccatgc accatggcat gccagagttc aacactgttg ctcttgaaaa ttgggtctga 420  
 aaaaacgcac aagagccctt gccctgccct agctganga c 461

<210> 325  
 <211> 400  
 <212> DNA  
 <213> Homo sapien

<400> 325  
 acaactgtttc catgttatgt ttctacacat tgctacctca gtgtcctgg aaacttagct 60  
 tttgatgtct ccaagtagtc caccttcatt taactctttg aaactgtatc atctttgcc 120  
 agtaagagtg gtggcctatt tcagctgctt tgacaaaatg actggctcct gacttaacgt 180  
 totataaatg aatgtgctga agcaaagtgc ccatgggtggc ggcgaagaag agaaagatgt 240  
 gttttgtttt ggactctctg tggctccctc caatgctgtg ggtttccaac caggggaagg 300  
 gtcccttttg cattgccaaag tgccataacc atgagcacta cgctaccatg gttctgctc 360  
 ctggccaagc aggtgtggtt gcaagaatga aatgaatgat 400

<210> 326  
 <211> 1215  
 <212> DNA  
 <213> Homo sapien

<400> 326  
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 gaactcctac accatcgggc tgggcctgca cagtcttgag gccgaccaag agccaggag 180  
 ccagatggtg gaggccagcc tctccgtacg gcacccagag tacaacagac ccttgctcgc 240  
 taacgacctc atgctcatca agttggacga atccgtgtcc gagtctgaca ccatccggag 300  
 catcagcatt gcttcgcagt gccctaccgc ggggaactct tgccctcgtt ctggctgggg 360  
 tctgctggcg aacggcagaa tgccctaccgt gctgcagtgc gtgaacgtgt cgggtggtgc 420  
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 cgggtacttg cagggccttg tgtctttcgg aaaagccccg tgtggccaag ttggcgtgcc 600  
 aggtgtctac accaactctt gcaaattcac tgagtggata gagaaaaccg tccaggccag 660  
 ttaactctgg ggaactgggaa cccatgaaat tgacccccaa atacatcctg cggaagggaat 720  
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gggccagacc cctcctccct cagaccaccg ggccaatgc cacctagact ctccctgtac 1080
acagtgcacc cttgtggcac gttgacccaa ccttaaccagt tgggttttca ttttttgtcc 1140
ttttcccta gatccagaaa taaagtctaa gagaagcgca aaaaaaaaaa aaaaaaaaaa 1200
aaaaaaaaa aaaaa 1215

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<210> 327  
 <211> 220  
 <212> PRT  
 <213> Homo sapien

```

<400> 327
Glu Asp Cys Ser Pro His Ser Gln Pro Trp Gln Ala Ala Leu Val Met
1      5      10      15
Glu Asn Glu Leu Phe Cys Ser Gly Val Leu Val His Pro Gln Trp Val
20     25     30
Leu Ser Ala Ala His Cys Phe Gln Asn Ser Tyr Thr Ile Gly Leu Gly
35     40     45
Leu His Ser Leu Glu Ala Asp Gln Glu Pro Gly Ser Gln Met Val Glu
50     55     60
Ala Ser Leu Ser Val Arg His Pro Glu Tyr Asn Arg Pro Leu Leu Ala
65     70     75     80
Asn Asp Leu Met Leu Ile Lys Leu Asp Glu Ser Val Ser Glu Ser Asp
85     90     95
Thr Ile Arg Ser Ile Ser Ile Ala Ser Gln Cys Pro Thr Ala Gly Asn
100    105    110
Ser Cys Leu Val Ser Gly Trp Gly Leu Leu Ala Asn Gly Arg Met Pro
115    120    125
Thr Val Leu Gln Cys Val Asn Val Ser Val Val Ser Glu Glu Val Cys
130    135    140
Ser Lys Leu Tyr Asp Pro Leu Tyr His Pro Ser Met Phe Cys Ala Gly
145    150    155    160
Gly Gly Gln Asp Gln Lys Asp Ser Cys Asn Gly Asp Ser Gly Gly Pro
165    170    175
Leu Ile Cys Asn Gly Tyr Leu Gln Gly Leu Val Ser Phe Gly Lys Ala
180    185    190
Pro Cys Gly Gln Val Gly Val Pro Gly Val Tyr Thr Asn Leu Cys Lys
195    200    205
Phe Thr Glu Trp Ile Glu Lys Thr Val Gln Ala Ser
210    215    220

```

<210> 328  
 <211> 234  
 <212> DNA  
 <213> Homo sapien

```

<400> 328
cgctcgtctc tggtagctgc agccaaatca taaacggcga ggactgcagc ccgcactcgc 60
agccctggca ggcggcactg gtcattgaaa acgaattgtt ctgctcgggc gtcctgggtgc 120
atccgcagtg ggtgctgtca gccacacact gtttcagaa ctctacacc atcgggctgg 180
gcctgcacag tcttgaggcc gaccaagagc caggagacca gatggtggag gccca 234

```

<210> 329  
 <211> 77  
 <212> PRT  
 <213> Homo sapien

```

<400> 329
Leu Val Ser Gly Ser Cys Ser Gln Ile Ile Asn Gly Glu Asp Cys Ser

```

1	5	10	15
Pro His Ser Gln	Pro Trp Gln Ala	Ala Leu Val Met Glu Asn Glu Leu	
	20	25	30
Phe Cys Ser Gly Val Leu Val His	Pro Gln Trp Val Leu Ser Ala Thr		
	35	40	45
His Cys Phe Gln Asn Ser Tyr Thr Ile Gly Leu Gly Leu His Ser Leu			
	50	55	60
Glu Ala Asp Gln Glu Pro Gly Ser Gln Met Val Glu Ala			
65	70	75	

<210> 330  
 <211> 70  
 <212> DNA  
 <213> Homo sapien

<400> 330  
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 gctgcagcca 70

<210> 331  
 <211> 22  
 <212> PRT  
 <213> Homo sapien

<400> 331  
 Gln His Asn Gly Pro Ile Pro Ser Leu Thr Pro Pro Ser Gly Ser Leu  
 1 5 10 15  
 Val Ser Gly Ser Cys Ser  
 20

<210> 332  
 <211> 2507  
 <212> DNA  
 <213> Homo sapien

<400> 332  
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 tgccttccct tctgtatatg gctgcgcccc aaatcaggaa aatgctgtcc agtgggggtg 120  
 gtacatcaac tgttcagctt octgggaaag tagttgtgtt cacaggagct aatacaggta 180  
 tcgggaagga gacagccaaa gagctggctc agagaggagc tcgagtatat ttagcttgcc 240  
 gggatgtgga aaagggggaa ttggtggcca aagagatcca gaccacgaca gggaaccagc 300  
 aggtgttggg ggggaaactg gacctgtctg atactaagtc tattcgagct tttgctaagg 360  
 gcttcttagc tgaggaaaag cacctccacg ttttgatcaa caatgcagga gtgatgatgt 420  
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 agaaattcta caatgcaggc ctggcctact gtcacagcaa gctagccaac atcctcttca 660  
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 ctagagatat cataatagga taagaagacc ctcatatgac ctgcacagct catttctctt 1260  
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aataaaaacg	taagaattaa	aagtttgatt	acaaaaaaa	aaaaaaa		2507

&lt;210&gt; 333

&lt;211&gt; 3030

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 333

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&lt;211&gt; 2984

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 335

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<400> 336

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Pro	Lys	Gln	Pro	Gln	Lys	Arg	Ser	Arg	Ala	Ala	Phe	Ser	His	Thr	Gln
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Pro	Glu	Arg	Ala	His	Leu	Ala	Lys	Asn	Leu	Lys	Leu	Thr	Glu	Thr	Gln
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 <213> Homo sapien

<400> 337

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<400> 338

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<210> 339  
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&lt;212&gt; PRT

&lt;213&gt; Homo sapien

&lt;400&gt; 339

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Cys Thr Ser Thr Val Gln Leu Pro Gly Lys Val Val Val Val Thr Gly
 35          40          45
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 50          55          60
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Val Ala Lys Glu Ile Gln Thr Thr Thr Gly Asn Gln Gln Val Leu Val
 85          90          95
Arg Lys Leu Asp Leu Ser Asp Thr Lys Ser Ile Arg Ala Phe Ala Lys
100          105          110
Gly Phe Leu Ala Glu Glu Lys His Leu His Val Leu Ile Asn Asn Ala
115          120          125
Gly Val Met Met Cys Pro Tyr Ser Lys Thr Ala Asp Gly Phe Glu Met
130          135          140
His Ile Gly Val Asn His Leu Gly His Phe Leu Leu Thr His Leu Leu
145          150          155          160
Leu Glu Lys Leu Lys Glu Ser Ala Pro Ser Arg Ile Val Asn Val Ser
165          170          175
Ser Leu Ala His His Leu Gly Arg Ile His Phe His Asn Leu Gln Gly
180          185          190
Glu Lys Phe Tyr Asn Ala Gly Leu Ala Tyr Cys His Ser Lys Leu Ala
195          200          205
Asn Ile Leu Phe Thr Gln Glu Leu Ala Arg Arg Leu Lys Gly Ser Gly
210          215          220
Val Thr Thr Tyr Ser Val His Pro Gly Thr Val Gln Ser Glu Leu Val
225          230          235          240
Arg His Ser Ser Phe Met Arg Trp Met Trp Trp Leu Phe Ser Phe Phe
245          250          255
Ile Lys Thr Pro Gln Gln Gly Ala Gln Thr Ser Leu His Cys Ala Leu
260          265          270
Thr Glu Gly Leu Glu Ile Leu Ser Gly Asn His Phe Ser Asp Cys His
275          280          285
Val Ala Trp Val Ser Ala Gln Ala Arg Asn Glu Thr Ile Ala Arg Arg
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Leu Trp Asp Val Ser Cys Asp Leu Leu Gly Leu Pro Ile Asp
305          310          315

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&lt;210&gt; 340

&lt;211&gt; 483

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 340

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gtttaggggg atgccaaagg taaggccagc tcagttatat gaagagaagc agaacaaca 180  
agtctttcag agaaatggat gcaatcagag tgggattccc gtcacatcaa ggtcacactc 240  
caccttcatg tgctgaatg gttgccaggc cagaaaaatc cacccttac gagtgcggct 300

```

tcgacctat atcccccgcc cgcgtccctt tctccataaa attcttctta gtagctatta 360
ctttcttatt atttgaicta gaaattgcc tctttttacc cctaccatga gccctacaaa 420
cuaactaacct gccactaata gttatgtcat cctcttatt aatcatcatc ctagccctaa 480
ctctggccta tgagtgaacta caaaaaggat tagactgagc cgaataacaa aaaaaa 536

```

```

<210> 345
<211> 251
<212> DNA
<213> Homo sapien

```

```

<400> 345
accttttqag gtctctctca ccacctccac agccaccgtc accgtgggat gtgctggatg 60
tgaatgaagg ccccatcttt gtgcctcctg aaaagagagt ggaagtgtcc gaggactttg 120
ggcggggcca ggaatcaca tctacactg cccaggagcc agacacattt atggaacaga 180
aaataacata tggatttgg agagacactg ccaactggct ggagattaat ccggacactg 240
gtgccatttc c
251

```

```

<210> 346
<211> 282
<212> DNA
<213> Homo sapien

```

```

<220>
<221> misc_feature
<222> (1)...(282)
<223> n = A,T,C or G

```

```

<400> 346
cgcgtctctg acactgtgat catgacaggg gttcaaacag aaagtgcctg ggccctcctt 60
ctaagtcttg ttaccaaaaa aaggaaaaag aaaagatctt ctcaattaca aattctggga 120
agggagacta tacctggctc ttgccttaag tgagaggtct tccctccgc accaaaaaat 180
agaaaggctt tctatttcac tggcccagg agggggaagg agagtaactt tgagtctgtg 240
ggtctcattt cccaagggtc cttcaatgct catnaaaacc aa 282

```

```

<210> 347
<211> 201
<212> DNA
<213> Homo sapien

```

```

<220>
<221> misc_feature
<222> (1)...(201)
<223> n = A,T,C or G

```

```

<400> 347
acacacataa tattataaaa tgccatctaa ttggaaggag ctttctatca ttgcaagtca 60
taaatataac ttttaaaana ntactancag cttttaccta ngctcctaaa tgcttgtaaa 120
tctgagactg actggacca cccagacca gggcaaagat acatgttacc atatcatctt 180
tataaagaat ttttttttgt c
201

```

```

<210> 348
<211> 251
<212> DNA
<213> Homo sapien

```

```

<400> 348
ctgttaatca caacatttgt gcatcacttg tgccaagtga gaaaatgttc taaaatcaca 60
agagagaaca gtgccagaat gaaactgacc ctaagtccca ggtgccctg ggcaggcaga 120

```

aggagacact	cccagcatgg	aggaggggtt	atcttttcat	cctaggtcag	gtctacaatg	180
ggggaagggt	ttattataga	actcccaaca	gccacctca	ctcctgccac	ccaccgatg	240
gccctgcctc	c					251

<210> 349  
 <211> 251  
 <212> DNA  
 <213> Homo sapien

<400> 349						
taaaaatcaa	gccattta	tgtatctttg	aaggtaaaca	atatatggga	gctggatcac	60
aacccctgag	gatgccagag	ctatgggtcc	agaacatgg	gtgggtattat	caacagagtt	120
cagaagggtc	tgaactctac	gtgttaccag	agaacataat	gcaattcatg	cattccactt	180
agcaattttg	taaaatacca	gaaacagacc	ccaagagtct	ttcaagatga	ggaaaattca	240
actcctgggt	t					251

<210> 350  
 <211> 908  
 <212> DNA  
 <213> Homo sapien

<400> 350						
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agccgcgccg	gtgaagctcg	ctgctttccc	tacctcctta	agtgactgcc	aaacgcccac	120
cggctggaat	tgtctgtggt	atgatgacag	agaaaatgat	ctcttcctct	gtgacaccaa	180
cacctgtaaa	tttgatgggg	aatgtttaag	aattggagac	actgtgactt	gcgtctgtca	240
gttcaagtgc	aacaatgact	atgtgcctgt	gtgtgggtcc	aatggggaga	gctaccagaa	300
tgagtgttac	ctgcgacagg	ctgcatgcaa	acagcagagt	gagatacttg	tggtgtcaga	360
aggatcatgt	gccacagtcc	atgaagggtc	tggagaaaact	agtcaaaagg	agacatccac	420
ctgtgatatt	tgccagtttg	gtgcagaatg	tgacgaagat	gccgaggatg	tctggtgtgt	480
gtgtaatat	gactgttctc	aaaccaactt	caatcccctc	tgcgcttctg	atgggaaatc	540
ttatgataat	gcatgccaaa	tcaaagaagc	atcgtgtcag	aaacaggaga	aaattgaagt	600
catgtctttg	ggtcgatgtc	aagataaac	aactacaact	actaagtctg	aagatgggca	660
ttatgcaaga	acagattatg	cagagaatgc	taacaaatta	gaagaaagtg	ccagagaaca	720
ccacatacct	tgtccggaac	attacaatgg	cttctgcatg	catgggaagt	gtgagcattc	780
tatcaatatg	caggagccat	cttgcaagg	tgatgctgg	tatactggac	aacactgtga	840
aaaaaaggac	tacagtgttc	tatacgttgt	tcccgggtcct	gtacgatttc	agtatgtctt	900
aatcgag						908

<210> 351  
 <211> 472  
 <212> DNA  
 <213> Homo sapien

<400> 351						
ccagttat	gcaagtgg	taagcctatt	taccataaat	aataactaaga	accaaactcaa	60
gtcaaacctt	aatgccattg	ttattgtgaa	ttaggattaa	gtagtaattt	tcaaaattca	120
cattaacttg	atttttaaa	cagwtttgyg	agtcatttac	cacaagctaa	atgtgtacac	180
tatgataaaa	acaaccattg	tattcctgtt	tttctaaaca	gtcctaattt	ctaactgt	240
atatatcctt	cgacatcaat	gaactttgtt	ttcttttact	ccagtaataa	agtaggcaca	300
gatctgtcca	caacaaactt	gccctctcat	gccttgccctc	tcaccatgct	ctgctccagg	360
tcagccccct	tttggcctgt	ttgttttgtc	aaaaacctaa	tctgtcttct	gcttttcttg	420
gtaatatata	tttagggaag	atgttgcttt	gccacacac	gaagcaaagt	aa	472

<210> 352  
 <211> 251  
 <212> DNA  
 <213> Homo sapien



&lt;400&gt; 352

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tg'ggataag	gccagggtcaa	tggetgcaag	catgcagaga	aagagggtaca	tcggagcgtg	120
cagcctgcgt	tcgcgtcotta	cgatgaagac	caagatgcag	tttccaaaca	ttgccactac	180
atacatggaa	aggaggggga	agccaaccca	gaaatgggct	ttctctaate	ctgggatacc	240
aataagcaca	a					251

&lt;210&gt; 353

&lt;211&gt; 436

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 353

tttttttttt	tttttttttt	tttttttaca	caatgcagtc	atatttttat	tgagtatgtg	60
cacattatgg	tattattact	atactgatta	tattttatcat	gtgacttcta	attaraaaat	120
gtatccaaaa	gcaaaacagc	agatatacaa	aattaaagag	acagaagata	gacattaaca	180
gataaggcaa	cttatacatt	gacaatccaa	atccaatata	tttaaacatt	tgggaaatga	240
gggggacaaa	tggaagccar	atcaaatttg	tgtaaaacta	ttcagtatgt	ttcccttgct	300
tcattgtctga	raaggctctc	ccttcaatgg	ggatgacaaa	ctccaaatgc	cacacaaatg	360
ttaacagaat	actagattca	cactggaacg	ggggtaaaga	agaaattatt	ttctataaaa	420
gggtccttaa	tgtaqt					436

&lt;210&gt; 354

&lt;211&gt; 854

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 354

ccttttctag	ttcaccagtt	ttctgcaagg	atgctgggta	gggagtgtct	gcaggaggag	60
caagtctgaa	accaaaatcta	ggaaacatag	gaaacgagcc	aggcacaggg	ctgggtgggc	120
atcagggacc	accctttggg	ttgatatttt	gcttaatctg	catcttttga	gtaagatcat	180
ctggcagtag	aagctgttct	ccagggtacat	ttctctagct	catgtacaaa	aacatcctga	240
aggactttgt	caggtgcctt	gctaaaagcc	agatgcgttc	ggcacttcct	tgggtctgagg	300
ttaattgcac	acctacaggc	actgggctca	tgctttcaag	tattttgtcc	tcacttttagg	360
gtgagtgaag	gatccccatt	ataggagcac	ttgggagaga	tcataataaa	gctgactcct	420
gagtacatgc	agtaatgggg	tagatgtgtg	tgggtgtgtc	tcattcctgc	aagggtgctt	480
gttagggagt	gtttccagga	ggaacaagtc	tgaaaccaat	catgaaataa	atggtaggtg	540
tgaactggaa	aactaattca	aaagagagat	cgtgatatca	gtgtggttga	tacaccttgg	600
caatatggaa	ggctctaatt	tgcccatatt	tgaaataata	attcagcttt	ttgtaataca	660
aaataacaaa	ggattgagaa	tcattggtgtc	taatgtataa	aagaccaggg	aaacataaat	720
atatcaactg	cataaatgta	aaatgcatgt	gacccaagaa	ggccccaag	tggcagacaa	780
cattgtaccc	attttccctt	ccaaaatgtg	agcggcgggc	ctgctgcttt	caaggctgtc	840
acacgggatg	tcag					854

&lt;210&gt; 355

&lt;211&gt; 676

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 355

gaaattaagt	atgagctaaa	ttccctgtta	aaacctctag	gggtgacaga	tctcttcaac	60
gaagtcacaa	ctgatctttc	tggaatgtca	ccaaccaagg	gcctatat	atcaaaagcc	120
atccacaagt	cataacctga	tgtcagcgaa	gagggcacgg	aggcagcagc	agccactggg	180
gacagcatcg	ctgtaaaaag	cctaccaatg	agagctcagt	tcaaggcgaa	ccacctcttc	240
ctgtctctta	taaggcacac	tcataccaac	acgatccat	tctgtggcaa	gcttgccctc	300
ccctaatacag	atgggggttg	gtaaggetca	gagttgcaga	tgagggtcag	agacaatcct	360
gtgactttcc	cacggccaaa	aagctgttca	cacctcacgc	acctctgtgc	ctcagtttgc	420

tcactctgcaa aataggtcta ggattttcttc caaccatttc atgagttgtg aagctaaggc	480
tttggttaate atggaaaaag gtagacttat gcagaaagcc tttctggctt tottatctgt	540
ggtgtctcat ttgagtgtctg tccagtgcac tgatcaagtc aatgagtaaa attttaaggg	600
attagatttt cttgacttgt atgtatctgt gagatcttga ataagtgacc tgacatctct	660
gcttaaagaa aaccag	676

&lt;210&gt; 356

&lt;211&gt; 574

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 356

tttttttttt tttttcagga aaacattctc ttactttatt tgcattctcag caaagggttct	60
catgtggcac ctgactggca tcaaaccaaa gtctgtaggc caacaaagat gggccactca	120
caagcttccc atttglagat ctcaagtgcct atgagtatct gacacctgtt cctctcttca	180
gtctcttaag gaggtctaaa tctgtctcag gtgtgctaag agtgccagcc caaggkggtc	240
aaaagtccac aaaactgcag tctttgctgg gatagtaagc caagcagtgc ctggacagca	300
gagttcttt ctggggcaac agataaccag acaggactct aatcgtgctc ttattcaaca	360
ttcttctgtc tctgcctaga ctggaataaa aagccaatct ctctcgtggc acagggaagg	420
agatacaagc tctgtttacat gtgatagatc taacaaaggc atctaccgaa gtctggctctg	480
gatagacggc acagggagct cttaggtcag cgctgctggt tggaggacat tcttgagtcc	540
agctttgcag cttttgtgca acagtacttt ccca	574

&lt;210&gt; 357

&lt;211&gt; 393

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 357

tttttttttt tttttttttt tttttttttt tacagaatat aratgcttta tcaactgkact	60
taatatggkg kcttggtcac tatacttaaa aatgcaccac tcataaatat ttaattcagc	120
aagccacaac caaracttga ttttatcaac aaaaaccctt aaatataaac ggsaaaaaag	180
atagatatata ttattccagt ttttttaaaa cttaaaarat attccattgc cgaattaara	240
araarataag tgttatatgg aaagaagggc attcaagcac actaaaraaa cctgaggkaa	300
gcataatctg tacaaaatta aactgtcctt tttggcattt taacaaattt gcaacgktct	360
tttttttctt tttctgtttt tttttttttt tac	393

&lt;210&gt; 358

&lt;211&gt; 630

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 358

acagggtaaa caggaggatc cttgctctca cggagcttac attctagcag gaggacaata	60
ttaatgttta taggaaaatg atgagtttat gacaaaggaa gtagatagtg ttttacaaga	120
gcatagagta ggaagctaa tccagcacag ggaggtcaca gagacatccc taagggaagt	180
gagtttaaac tgagagaagc aagtgcctaa actgaaggat gtgttgaaga agaagggaga	240
gtagaacaat ttgggcagag ggaaccttat agaccctaag gtgggaagggt tcaaagaact	300
gaaagagagc tagaacagct ggagccgttc tccggtgtaa agaggagtca aagagataag	360
attaaagatg tgaagattaa gatcttggtg gcattcagg attggcactt ctacaagaaa	420
tcaactgaagg gagtaatgtg acattacttt tcaactcagg atggccattc taactccagg	480
ggtagactg gactaggtaa gactggaggc aggtagacct cttctaaggc ctgcgatagt	540
gaaagacaaa aataagtggg gaaattcagg ggatagtga aatcagtagg acttaatgag	600
caagccagag gttcctccac aacaaccagt	630

&lt;210&gt; 359

&lt;211&gt; 620

&lt;212&gt; DNA

atagcattcc	aaaatataca	tctagagact	aarrgtaaat	gctctatagt	gaagaagtaa	60
taattaaaaa	atgctactaa	tatagaaaat	ttataatcag	aaaaataaat	attcagggag	120
ctcaccagaa	gaataaagtg	ctctgccagt	tattaaagga	ttactgctgg	tgaattaaat	180
atggcattcc	caaagggaaa	tagagagatt	cttctggatt	atgttcaata	tttattttcac	240
aggattaaact	gttttaggaa	cagatataaa	gcttcgccac	ggaagagatg	gacaaagcac	300
aaagacaaca	tgatacctta	ggaagcaaca	ctaccctttc	aggcataaaa	tttggaagaaa	360
tgcacatta	tgtttcatga	ataatatgta	gaaagaaggt	ctgatgaaaa	tgacatcctt	420
aatgtaagat	aacttttata	gaattctggg	tcaaataaaa	ttctttgaag	aaaacatcca	480
aatgtcattg	actttatcaa	tactatcttg	gcataatacc	tatgaaggca	aaactaaca	540
aacaaaaagc	tcacacaaaa	caaaaccatc	aacttatttt	gtattctata	acatacgaga	600
ctgtaaaagat	gtgacagttt					620

<213> Homo sapien

agagagaaaa	agccagaaca	acatgtgata	gataatatga	ttggtctcac	acttcagac	60
tgaatgaatga	tgaacgtgat	ggactattgt	atggagcaca	tcttcagcaa	gagggggaaa	120
laattcatcat	ttttggccag	cagttgtttg	atcaccaaac	atcatgccag	aatactcagc	180
aaaccttctt	agctcttgag	aagtcaaagt	ccgggggaat	ttattcctgg	caattttaat	240
tggactcctt	atgtgagagc	agcggctacc	cagctggggt	ggtggagcga	acccgtcact	300
agtggacatg	cagtggcaga	gctctggta	accacctaga	ggaatacaca	ggcacatgtg	360
tgaatgccaa	cgtagacacct	gtagcactca	aatttgtctt	gtttttgtct	ttcgggtgtgt	420
gaattcttta	t					431

<213> Homo sapien

gcactgattt	cogatcaaaa	gaatcatcat	ctttaccttg	acttttcagg	gaattactga	60
acttttcttct	cagaagatag	ggcacagcca	ttgccttggc	ctcacttgaa	gggtctgcat	120
ttgggtctctc	tggtctcttg	ccaagtttcc	cagccaactcg	agggagaaat	atcgggaggt	180
ttgacttctct	ccggggcttt	cccaggggtc	tcacctgtag	ccctgcggcc	ctcagggctg	240
caactctgga	ttcaattgtct	gaaacctcgc	ttctgtcctg	cttgcacttct	gaggccgtca	300
ctgccactct	gtcctccage	tctgacagct	cctcatctgt	ggtcctgttg	t	351

<213> Homo sapien

acttcacag	gccataatgg	gtgcctcccg	tgagaatcca	agcacctttg	gactgcgcga	60
tgtagatgag	ccggetgaag	atcttgcgca	tgcgcggett	cagggcggaag	ttcttggcgc	120
cccgggtcac	agaaatgacc	aggttgggtg	tttccaggtg	ccagtgtctg	gtcagcagct	180
cgtaaaggat	ttccgcgtcc	gtgtcgcagg	acagacgtat	atacttccct	ttcttcccca	240
gtgtctcaaa	ctgaatatcc	ccaaaggcgt	cggtaggaaa	ttccttggtg	tgtttcttgt	300
agttccattt	ctcacttttg	ttgatctcgg	tgccttccat	gtgctggctc	tgggcatagc	360
caactttgca	cacattttcc	ctgataagca	cgatggtgtg	gacaggaagg	aaggatttca	420
tggaccttgc	ttatgaaaac	tggatttgtt	acgttaataa	gac		463

<210> 363  
 <211> 653  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(653)  
 <223> n = A,T,C or G

<400> 363  
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 ctcttgngga ttctgggtga catcttcatg aatggcaacc gtgccagwga ggctgtcctc 120  
 tgggaggcac tacgcaagat gggactgcgt cctgggggtga gacatcctct ccttggagat 180  
 ctaacgaaac ttctcaccta tgagttgtaa agcagaaata cctgnactac agacgagtgc 240  
 ccaacagcaa ccccccgga gtatgagttc ctctrgggcc tccgttccta ccatgagasc 300  
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 ctgaggccga agcccgggct gaagcaagaa cccgcattgg aattggagat gaggtgtgt 480  
 ntgggcccctg gagctgggat gacattgagt ttgagctgct gacctgggat gaggaaggag 540  
 attttggaga tccntgggcc agaattccat ttaccttctg ggccagatac caccagaatg 600  
 cccgctccag attcctcag acctttgccg gtcccattat tggctcstggg ggt 653

<210> 364  
 <211> 401  
 <212> DNA  
 <213> Homo sapien

<400> 364  
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 aaaacaagggt ggatagatct agaattgtaa cattttaaga aaaccatagc atttgacaga 180  
 tgagaaagct caattataga tgcaaagtta taactaaact actatagtag taaagaaata 240  
 catttcacac ccttcatata aattcaactat ctgggcttga ggcactccat aaaatgtatc 300  
 acgtgcatag taaatcttta tatttgctat ggcgttgca tagaggactt ggactgcaac 360  
 aagtggatgc gcggaatg aaatcttctt caatagccca g 401

<210> 365  
 <211> 356  
 <212> DNA  
 <213> Homo sapien

<400> 365  
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 taccagagca tcaagtctct gcagcaggtc attcttgggt aaagaaatga ctccacaaa 180  
 ctctccatcc cctggctttg gcttcggcct tgcgttttcg gcatcatctc cgttaatggt 240  
 gactgtcacg atgtgtatag tacagtttga caagcctggg tccatacaga ccgctggaga 300  
 acattcggca atgtcccctt tgtagccagt ttcttcttcg agctcccgga gagcag 356

<210> 366  
 <211> 1851  
 <212> DNA  
 <213> Homo sapien

<400> 366  
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 cttccgtgtt cttcattctt cttcaatagc cataaatctt ctagctctgg ctggctgttt 120

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teacttcectt taagcctttg tgactcttcc tctgatgtca gctttaagtc ttgttctgga 180
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aaaattacat gatgatgact agaaacagca tactctctgg ccgtctttcc agatcttgag 300
aagatacatc aacattttgc tcaagtagag ggctgactat acttgcctgat ccacaacata 360
cagcaagtat gagagcagtt ctcccatatc tatccagcgc atttaaattc gcttttttct 420
tgattaaaaa tttcaccact tgctgttttt gctcatgtat accaagtage agtgggtgtga 480
gcccattgctt gttttttgat tcgatatcag caccgtataa gagcagtgct ttggccatta 540
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ttggatcagt gccatgttcc agcaacatta acgcacattc atcttctctg cattgtacgg 660
cctttgtcag agctgtcctc tttttgttgt caaggacatt aagttgacat cgtctgtcca 720
gcacagagtt tactacttct gaattcccat tggcagaggc cagatgtaga gcagtcctct 780
tttgcttgtc cctcttggtc acatccgtgt ccttgagcat gacgatgaga tcttttctgg 840
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&lt;210&gt; 367

&lt;211&gt; 668

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 367

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&lt;210&gt; 368

&lt;211&gt; 1512

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 368

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&lt;210&gt; 369

&lt;211&gt; 1853

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 369

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ccagcctggg tgacagagca agactctgtc tcaaaaaaaaa aaaaaaaaaa aaa 1853

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<210> 370
<211> 2184
<212> DNA
<213> Homo sapien

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<400> 370
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<210> 371
<211> 1855
<212> DNA
<213> Homo sapien

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<223> n = A,T,C or G

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&lt;400&gt; 371

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&lt;210&gt; 372

&lt;211&gt; 1059

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 372

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 <212> DNA  
 <213> Homo sapien

<400> 373

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<210> 374  
 <211> 2000  
 <212> DNA  
 <213> Homo sapien

<400> 374

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ctggatagat	atggaaggac	tgctctcata	cttgcgtgat	gttgtggatc	agcaagtata	960
gtcagccttc	tacttgagca	aaatattgat	gtatcttctc	aagatctatc	tggacagacg	1020
gccagagagt	atgctgtttc	tagtcatcat	catgtaattt	gccagttact	ttctgactac	1080
aaagaaaaac	agatgctaaa	aatctcttct	gaaaacagca	atccagaaca	agacttaag	1140
ctgacatcag	aggaagagtc	acaaagggttc	aaaggcagtg	aaaatagcca	gccagagaaa	1200
atgtctcaag	aaccagaaat	aaataaggat	ggtgatagag	aggttgaaga	agaaatgaag	1260
aagcatgaaa	gtaataatgt	gggattacta	gaaaacctga	ctaattggtgt	cactgctggc	1320
aatggtgata	atggattaat	tcctcaaagg	aagagcagaa	cacctgaaaa	tcagcaattt	1380
cctgacaacg	aaagtgaaga	gtatcacaga	atttgcgaat	tagtttctga	ctacaaagaa	1440
aaacagatgc	caaaatactc	ttctgaaaaac	agcaaccag	aacaagactt	aaagctgaca	1500

tcagaggaag	agtcacaaag	gcttgagggc	agtgaaaatg	gccagccaga	gctagaaaat	1560
tttatggcta	tcgaagaaat	gaagaagcac	ggaagtactc	atgtcggatt	cccagaaaac	1620
ctgactaatg	gtgccactgc	tggaatgggt	gatgatggat	taattcctcc	aaggaagagc	1680
agaacacctg	aaagccagca	atttcctgac	actgagaatg	aagagtatca	cagtgaacgaa	1740
caaaatgata	ctcagaagca	attttgtgaa	<b>gaacagaaca</b>	<b>ctggaatatt</b>	<b>acacgatgag</b>	<b>1800</b>
attctgattc	atgaagaaaa	gcagatagaa	gtggttgaaa	aaatgaattc	tgagctttct	1860
cttagttgta	agaaagaaaa	agacatcttg	catgaaaata	gtacgttgcg	ggaagaaatt	1920
gccatgctaa	gactggagct	agacacaatg	aaacatcaga	gccagctaaa	aaaaaaaaaa	1980
aaaaaaaaaa	aaaaaaaaaa					2000

&lt;210&gt; 375

&lt;211&gt; 2040

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 375

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aggagcaaga	tgggcaagtg	gtgctgccgt	tgtctccctc	gctgcaggga	gagcggaag	120
agcaacgtgg	gcacttctgg	agaccacgac	gactctgcta	tgaagacact	caggagcaag	180
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tgggtgctgcc	actgcttccc	ctgctgcagg	gggagcggca	agagcaaggt	gggcgcttgg	360
ggagactacg	atgacagtgc	cttcatggag	cccagggtacc	acgtccgtgg	agaagatctg	420
gacaagctcc	acagagctgc	ctggtggggg	aaagtcccca	gaaaggatct	catcgctcatg	480
ctcagggaca	ctgacgtgaa	caagaaggac	aagcaaaaaga	ggactgctct	acatctggcc	540
tctgccaatg	ggaattcaga	agtagtaaaa	ctcctgctgg	acagacgatg	tcaacttaat	600
gtccttgaca	acaaaaagag	gacagctctg	ataaaggccg	tacaatgcca	ggaagatgaa	660
tgtgcgttaa	tgttgctgga	acatggcact	gatccaaata	ttccagatga	gtatggaaat	720
accactctgc	actacgctat	ctataatgaa	gataaattaa	tggccaaagc	actgctctta	780
tatggtgctg	atatcgaaatc	aaaaaacaag	catggcctca	caccactgtt	acttgggtgta	840
catgagcaaa	aacagcaagt	cgtgaaatth	ttaatcaaga	aaaaagcgaa	tttaaatgca	900
ctggatagat	atggaaggac	tgtctctcata	cttgcctgtat	gttgtggatc	agcaagtata	960
gtcagccttc	tacttgagca	aaatattgat	gtatcttctc	aagatctatc	tggacagacg	1020
gccagagagt	atgctgtttc	tagtcatcat	catgtaatth	gccagttact	ttctgactac	1080
aaagaaaaac	agatgctaaa	aatctcttct	gaaaacagca	atccagaaca	agacttaag	1140
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cctgacaacg	aaagtgaaga	gtatcacaga	atttgcgaat	tagtttctga	ctacaaagaa	1440
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caagaaccag	aaataaataa	ggatggtgat	agagagctag	aaaattttat	ggctatcgaa	1620
gaaatgaaga	agcacggaag	tactcatgtc	ggattcccag	aaaacctgac	taatggtgcc	1680
actgctggca	atggtgatga	tggattaatt	cctccaagga	agagcagaac	acctgaaagc	1740
cagcaatthc	ctgacactga	gaatgaagag	tatcacagtg	acgaacaaaa	tgatactcag	1800
aagcaatthh	gtgaagaaca	gaacactgga	atattacacg	atgagattct	gattcatgaa	1860
gaaaagcaga	tagaagtggg	tgaaaaaatg	aattctgagc	tttctcttag	ttgtaagaaa	1920
gaaaagaca	tcttgcatga	aaatagtacg	ttgcgggaag	aaattgccat	gctaagactg	1980
gagctagaca	caatgaaaca	tcagagccag	ctaaaaaaaa	aaaaaaaaaa	aaaaaaaaaa	2040

&lt;210&gt; 376

&lt;211&gt; 329

&lt;212&gt; PRT

&lt;213&gt; Homo sapien

&lt;400&gt; 376

Met Asp Ile Val Val Ser Gly Ser His Pro Leu Trp Val Asp Ser Phe

[illegible]

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<210> 377
<211> 148
<212> PRT
<213> Homo sapien
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<221> VARIANT  
<222> (1)...(148)  
<223> Xaa = Any Amino Acid
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<400> 377															
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Trp	Thr	Ser	Ser	Thr	Glu	Leu	Pro	Trp	Trp	Gly	Lys	Val	Pro	Arg	Lys
			20					25					30		
Asp	Leu	Ile	Val	Met	Leu	Arg	Asp	Thr	Asp	Val	Asn	Lys	Xaa	Asp	Lys

35 40 45  
 Gln Lys Arg Thr Ala Leu His Leu Ala Ser Ala Asn Gly Asn Ser Glu  
 50 55 60  
 Val Val Lys Leu Xaa Leu Asp Arg Arg Cys Gln Leu Asn Val Leu Asp  
 65 70 75 80  
 Asn Lys Lys Arg Thr Ala Leu Xaa Lys Ala Val Gln Cys Gln Glu Asp  
 85 90 95  
 Glu Cys Ala Leu Met Leu Leu Glu His Gly Thr Asp Pro Asn Ile Pro  
 100 105 110  
 Asp Glu Tyr Gly Asn Thr Thr Leu His Tyr Ala Xaa Tyr Asn Glu Asp  
 115 120 125  
 Lys Leu Met Ala Lys Ala Leu Leu Tyr Gly Ala Asp Ile Glu Ser  
 130 135 140  
 Lys Asn Lys Val  
 145

<210> 378  
 <211> 1719  
 <212> PRT  
 <213> Homo sapien

<400> 378  
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 20 25 30  
 Pro Cys Cys Arg Glu Ser Gly Lys Ser Asn Val Gly Thr Ser Gly Asp  
 35 40 45  
 His Asp Asp Ser Ala Met Lys Thr Leu Arg Ser Lys Met Gly Lys Trp  
 50 55 60  
 Cys Arg His Cys Phe Pro Cys Cys Arg Gly Ser Gly Lys Ser Asn Val  
 65 70 75 80  
 Gly Ala Ser Gly Asp His Asp Asp Ser Ala Met Lys Thr Leu Arg Asn  
 85 90 95  
 Lys Met Gly Lys Trp Cys Cys His Cys Phe Pro Cys Cys Arg Gly Ser  
 100 105 110  
 Gly Lys Ser Lys Val Gly Ala Trp Gly Asp Tyr Asp Asp Ser Ala Phe  
 115 120 125  
 Met Glu Pro Arg Tyr His Val Arg Gly Glu Asp Leu Asp Lys Leu His  
 130 135 140  
 Arg Ala Ala Trp Trp Gly Lys Val Pro Arg Lys Asp Leu Ile Val Met  
 145 150 155 160  
 Leu Arg Asp Thr Asp Val Asn Lys Lys Asp Lys Gln Lys Arg Thr Ala  
 165 170 175  
 Leu His Leu Ala Ser Ala Asn Gly Asn Ser Glu Val Val Lys Leu Leu  
 180 185 190  
 Leu Asp Arg Arg Cys Gln Leu Asn Val Leu Asp Asn Lys Lys Arg Thr  
 195 200 205  
 Ala Leu Ile Lys Ala Val Gln Cys Gln Glu Asp Glu Cys Ala Leu Met  
 210 215 220  
 Leu Leu Glu His Gly Thr Asp Pro Asn Ile Pro Asp Glu Tyr Gly Asn  
 225 230 235 240  
 Thr Thr Leu His Tyr Ala Ile Tyr Asn Glu Asp Lys Leu Met Ala Lys  
 245 250 255  
 Ala Leu Leu Leu Tyr Gly Ala Asp Ile Glu Ser Lys Asn Lys His Gly  
 260 265 270  
 Leu Thr Pro Leu Leu Leu Gly Val His Glu Gln Lys Gln Gln Val Val  
 275 280 285

Lys	Phe	Leu	Ile	Lys	Lys	Lys	Ala	Asn	Leu	Asn	Ala	Leu	Asp	Arg	Tyr
290						295				300					
Gly	Arg	Thr	Ala	Leu	Ile	Leu	Ala	Val	Cys	Cys	Gly	Ser	Ala	Ser	Ile
305					310					315					320
Val	Ser	Leu	Leu	Leu	Glu	Gln	Asn	Ile	Asp	Val	Ser	Ser	Gln	Asp	Leu
				325					330					335	
Ser	Gly	Gln	Thr	Ala	Arg	Glu	Tyr	Ala	Val	Ser	Ser	His	His	His	Val
			340					345					350		
Ile	Cys	Gln	Leu	Leu	Ser	Asp	Tyr	Lys	Glu	Lys	Gln	Met	Leu	Lys	Ile
		355					360					365			
Ser	Ser	Glu	Asn	Ser	Asn	Pro	Glu	Asn	Val	Ser	Arg	Thr	Arg	Asn	Lys
		370				375					380				
Pro	Arg	Thr	His	Met	Val	Val	Glu	Val	Asp	Ser	Met	Pro	Ala	Ala	Ser
385					390						395				400
Ser	Val	Lys	Lys	Pro	Phe	Gly	Leu	Arg	Ser	Lys	Met	Gly	Lys	Trp	Cys
				405					410					415	
Cys	Arg	Cys	Phe	Pro	Cys	Cys	Arg	Glu	Ser	Gly	Lys	Ser	Asn	Val	Gly
			420					425					430		
Thr	Ser	Gly	Asp	His	Asp	Asp	Ser	Ala	Met	Lys	Thr	Leu	Arg	Ser	Lys
		435					440					445			
Met	Gly	Lys	Trp	Cys	Arg	His	Cys	Phe	Pro	Cys	Cys	Arg	Gly	Ser	Gly
		450				455					460				
Lys	Ser	Asn	Val	Gly	Ala	Ser	Gly	Asp	His	Asp	Asp	Ser	Ala	Met	Lys
465					470					475					480
Thr	Leu	Arg	Asn	Lys	Met	Gly	Lys	Trp	Cys	Cys	His	Cys	Phe	Pro	Cys
				485					490					495	
Cys	Arg	Gly	Ser	Gly	Lys	Ser	Lys	Val	Gly	Ala	Trp	Gly	Asp	Tyr	Asp
			500					505					510		
Asp	Ser	Ala	Phe	Met	Glu	Pro	Arg	Tyr	His	Val	Arg	Gly	Glu	Asp	Leu
		515					520					525			
Asp	Lys	Leu	His	Arg	Ala	Ala	Trp	Trp	Gly	Lys	Val	Pro	Arg	Lys	Asp
		530				535					540				
Leu	Ile	Val	Met	Leu	Arg	Asp	Thr	Asp	Val	Asn	Lys	Lys	Asp	Lys	Gln
545					550					555					560
Lys	Arg	Thr	Ala	Leu	His	Leu	Ala	Ser	Ala	Asn	Gly	Asn	Ser	Glu	Val
				565					570					575	
Val	Lys	Leu	Leu	Leu	Asp	Arg	Arg	Cys	Gln	Leu	Asn	Val	Leu	Asp	Asn
			580					585					590		
Lys	Lys	Arg	Thr	Ala	Leu	Ile	Lys	Ala	Val	Gln	Cys	Gln	Glu	Asp	Glu
		595					600					605			
Cys	Ala	Leu	Met	Leu	Leu	Glu	His	Gly	Thr	Asp	Pro	Asn	Ile	Pro	Asp
		610				615					620				
Glu	Tyr	Gly	Asn	Thr	Thr	Leu	His	Tyr	Ala	Ile	Tyr	Asn	Glu	Asp	Lys
625					630					635					640
Leu	Met	Ala	Lys	Ala	Leu	Leu	Leu	Tyr	Gly	Ala	Asp	Ile	Glu	Ser	Lys
				645					650					655	
Asn	Lys	His	Gly	Leu	Thr	Pro	Leu	Leu	Leu	Gly	Val	His	Glu	Gln	Lys
			660					665					670		
Gln	Gln	Val	Val	Lys	Phe	Leu	Ile	Lys	Lys	Lys	Ala	Asn	Leu	Asn	Ala
		675					680					685			
Leu	Asp	Arg	Tyr	Gly	Arg	Thr	Ala	Leu	Ile	Leu	Ala	Val	Cys	Cys	Gly
		690				695					700				
Ser	Ala	Ser	Ile	Val	Ser	Leu	Leu	Leu	Glu	Gln	Asn	Ile	Asp	Val	Ser
705					710					715					720
Ser	Gln	Asp	Leu	Ser	Gly	Gln	Thr	Ala	Arg	Glu	Tyr	Ala	Val	Ser	Ser
			725						730					735	
His	His	His	Val	Ile	Cys	Gln	Leu	Leu	Ser	Asp	Tyr	Lys	Glu	Lys	Gln
			740					745					750		

Met Leu Lys Ile Ser Ser Glu Asn Ser Asn Pro Glu Gln Asp Leu Lys  
 755 760 765  
 Leu Thr Ser Glu Glu Glu Ser Gln Arg Phe Lys Gly Ser Glu Asn Ser  
 770 775 780  
 Gln Pro Glu Lys Met Ser Gln Glu Pro Glu Ile Asn Lys Asp Gly Asp  
 785 790 795 800  
 Arg Glu Val Glu Glu Glu Met Lys Lys His Glu Ser Asn Asn Val Gly  
 805 810 815  
 Leu Leu Glu Asn Leu Thr Asn Gly Val Thr Ala Gly Asn Gly Asp Asn  
 820 825 830  
 Gly Leu Ile Pro Gln Arg Lys Ser Arg Thr Pro Glu Asn Gln Gln Phe  
 835 840 845  
 Pro Asp Asn Glu Ser Glu Glu Tyr His Arg Ile Cys Glu Leu Val Ser  
 850 855 860  
 Asp Tyr Lys Glu Lys Gln Met Pro Lys Tyr Ser Ser Glu Asn Ser Asn  
 865 870 875 880  
 Pro Glu Gln Asp Leu Lys Leu Thr Ser Glu Glu Glu Ser Gln Arg Leu  
 885 890 895  
 Glu Gly Ser Glu Asn Gly Gln Pro Glu Leu Glu Asn Phe Met Ala Ile  
 900 905 910  
 Glu Glu Met Lys Lys His Gly Ser Thr His Val Gly Phe Pro Glu Asn  
 915 920 925  
 Leu Thr Asn Gly Ala Thr Ala Gly Asn Gly Asp Asp Gly Leu Ile Pro  
 930 935 940  
 Pro Arg Lys Ser Arg Thr Pro Glu Ser Gln Gln Phe Pro Asp Thr Glu  
 945 950 955 960  
 Asn Glu Glu Tyr His Ser Asp Glu Gln Asn Asp Thr Gln Lys Gln Phe  
 965 970 975  
 Cys Glu Glu Gln Asn Thr Gly Ile Leu His Asp Glu Ile Leu Ile His  
 980 985 990  
 Glu Glu Lys Gln Ile Glu Val Val Glu Lys Met Asn Ser Glu Leu Ser  
 995 1000 1005  
 Leu Ser Cys Lys Lys Glu Lys Asp Ile Leu His Glu Asn Ser Thr Leu  
 1010 1015 1020  
 Arg Glu Glu Ile Ala Met Leu Arg Leu Glu Leu Asp Thr Met Lys His  
 1025 1030 1035 1040  
 Gln Ser Gln Leu Pro Arg Thr His Met Val Val Glu Val Asp Ser Met  
 1045 1050 1055  
 Pro Ala Ala Ser Ser Val Lys Lys Pro Phe Gly Leu Arg Ser Lys Met  
 1060 1065 1070  
 Gly Lys Trp Cys Cys Arg Cys Phe Pro Cys Cys Arg Glu Ser Gly Lys  
 1075 1080 1085  
 Ser Asn Val Gly Thr Ser Gly Asp His Asp Asp Ser Ala Met Lys Thr  
 1090 1095 1100  
 Leu Arg Ser Lys Met Gly Lys Trp Cys Arg His Cys Phe Pro Cys Cys  
 1105 1110 1115 1120  
 Arg Gly Ser Gly Lys Ser Asn Val Gly Ala Ser Gly Asp His Asp Asp  
 1125 1130 1135  
 Ser Ala Met Lys Thr Leu Arg Asn Lys Met Gly Lys Trp Cys Cys His  
 1140 1145 1150  
 Cys Phe Pro Cys Cys Arg Gly Ser Gly Lys Ser Lys Val Gly Ala Trp  
 1155 1160 1165  
 Gly Asp Tyr Asp Asp Ser Ala Phe Met Glu Pro Arg Tyr His Val Arg  
 1170 1175 1180  
 Gly Glu Asp Leu Asp Lys Leu His Arg Ala Ala Trp Trp Gly Lys Val  
 1185 1190 1195 1200  
 Pro Arg Lys Asp Leu Ile Val Met Leu Arg Asp Thr Asp Val Asn Lys  
 1205 1210 1215

Lys Asp Lys Gln Lys Arg Thr Ala Leu His Leu Ala Ser Ala Asn Gly  
 1220 1225 1230  
 Asn Ser Glu Val Val Lys Leu Leu Asp Arg Arg Cys Gln Leu Asn  
 1235 1240 1245  
 Val Leu Asp Asn Lys Lys Arg Thr Ala Leu Ile Lys Ala Val Gln Cys  
 1250 1255 1260  
 Gln Glu Asp Glu Cys Ala Leu Met Leu Leu Glu His Gly Thr Asp Pro  
 1265 1270 1275 1280  
 Asn Ile Pro Asp Glu Tyr Gly Asn Thr Thr Leu His Tyr Ala Ile Tyr  
 1285 1290 1295  
 Asn Glu Asp Lys Leu Met Ala Lys Ala Leu Leu Leu Tyr Gly Ala Asp  
 1300 1305 1310  
 Ile Glu Ser Lys Asn Lys His Gly Leu Thr Pro Leu Leu Leu Gly Val  
 1315 1320 1325  
 His Glu Gln Lys Gln Gln Val Val Lys Phe Leu Ile Lys Lys Lys Ala  
 1330 1335 1340  
 Asn Leu Asn Ala Leu Asp Arg Tyr Gly Arg Thr Ala Leu Ile Leu Ala  
 1345 1350 1355 1360  
 Val Cys Cys Gly Ser Ala Ser Ile Val Ser Leu Leu Leu Glu Gln Asn  
 1365 1370 1375  
 Ile Asp Val Ser Ser Gln Asp Leu Ser Gly Gln Thr Ala Arg Glu Tyr  
 1380 1385 1390  
 Ala Val Ser Ser His His His Val Ile Cys Gln Leu Leu Ser Asp Tyr  
 1395 1400 1405  
 Lys Glu Lys Gln Met Leu Lys Ile Ser Ser Glu Asn Ser Asn Pro Glu  
 1410 1415 1420  
 Gln Asp Leu Lys Leu Thr Ser Glu Glu Glu Ser Gln Arg Phe Lys Gly  
 1425 1430 1435 1440  
 Ser Glu Asn Ser Gln Pro Glu Lys Met Ser Gln Glu Pro Glu Ile Asn  
 1445 1450 1455  
 Lys Asp Gly Asp Arg Glu Val Glu Glu Glu Met Lys Lys His Glu Ser  
 1460 1465 1470  
 Asn Asn Val Gly Leu Leu Glu Asn Leu Thr Asn Gly Val Thr Ala Gly  
 1475 1480 1485  
 Asn Gly Asp Asn Gly Leu Ile Pro Gln Arg Lys Ser Arg Thr Pro Glu  
 1490 1495 1500  
 Asn Gln Gln Phe Pro Asp Asn Glu Ser Glu Glu Tyr His Arg Ile Cys  
 1505 1510 1515 1520  
 Glu Leu Val Ser Asp Tyr Lys Glu Lys Gln Met Pro Lys Tyr Ser Ser  
 1525 1530 1535  
 Glu Asn Ser Asn Pro Glu Gln Asp Leu Lys Leu Thr Ser Glu Glu Glu  
 1540 1545 1550  
 Ser Gln Arg Leu Glu Gly Ser Glu Asn Gly Gln Pro Glu Lys Arg Ser  
 1555 1560 1565  
 Gln Glu Pro Glu Ile Asn Lys Asp Gly Asp Arg Glu Leu Glu Asn Phe  
 1570 1575 1580  
 Met Ala Ile Glu Glu Met Lys Lys His Gly Ser Thr His Val Gly Phe  
 1585 1590 1595 1600  
 Pro Glu Asn Leu Thr Asn Gly Ala Thr Ala Gly Asn Gly Asp Asp Gly  
 1605 1610 1615  
 Leu Ile Pro Pro Arg Lys Ser Arg Thr Pro Glu Ser Gln Gln Phe Pro  
 1620 1625 1630  
 Asp Thr Glu Asn Glu Glu Tyr His Ser Asp Glu Gln Asn Asp Thr Gln  
 1635 1640 1645  
 Lys Gln Phe Cys Glu Glu Gln Asn Thr Gly Ile Leu His Asp Glu Ile  
 1650 1655 1660  
 Leu Ile His Glu Glu Lys Gln Ile Glu Val Val Glu Lys Met Asn Ser  
 1665 1670 1675 1680

Glu Leu Ser Leu Ser Cys Lys Lys Glu Lys Asp Ile Leu His Glu Asn  
 1685 1690 1695  
 Ser Thr Leu Arg Glu Glu Ile Ala Met Leu Arg Leu Glu Leu Asp Thr  
 1700 1705 1710  
 Met Lys His Gln Ser Gln Leu  
 1715

<210> 379  
 <211> 656  
 <212> PRT  
 <213> Homo sapien

<400> 379  
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 20 25 30  
 Pro Cys Cys Arg Glu Ser Gly Lys Ser Asn Val Gly Thr Ser Gly Asp  
 35 40 45  
 His Asp Asp Ser Ala Met Lys Thr Leu Arg Ser Lys Met Gly Lys Trp  
 50 55 60  
 Cys Arg His Cys Phe Pro Cys Cys Arg Gly Ser Gly Lys Ser Asn Val  
 65 70 75 80  
 Gly Ala Ser Gly Asp His Asp Asp Ser Ala Met Lys Thr Leu Arg Asn  
 85 90 95  
 Lys Met Gly Lys Trp Cys Cys His Cys Phe Pro Cys Cys Arg Gly Ser  
 100 105 110  
 Gly Lys Ser Lys Val Gly Ala Trp Gly Asp Tyr Asp Asp Ser Ala Phe  
 115 120 125  
 Met Glu Pro Arg Tyr His Val Arg Gly Glu Asp Leu Asp Lys Leu His  
 130 135 140  
 Arg Ala Ala Trp Trp Gly Lys Val Pro Arg Lys Asp Leu Ile Val Met  
 145 150 155 160  
 Leu Arg Asp Thr Asp Val Asn Lys Lys Asp Lys Gln Lys Arg Thr Ala  
 165 170 175  
 Leu His Leu Ala Ser Ala Asn Gly Asn Ser Glu Val Val Lys Leu Leu  
 180 185 190  
 Leu Asp Arg Arg Cys Gln Leu Asn Val Leu Asp Asn Lys Lys Arg Thr  
 195 200 205  
 Ala Leu Ile Lys Ala Val Gln Cys Gln Glu Asp Glu Cys Ala Leu Met  
 210 215 220  
 Leu Leu Glu His Gly Thr Asp Pro Asn Ile Pro Asp Glu Tyr Gly Asn  
 225 230 235 240  
 Thr Thr Leu His Tyr Ala Ile Tyr Asn Glu Asp Lys Leu Met Ala Lys  
 245 250 255  
 Ala Leu Leu Leu Tyr Gly Ala Asp Ile Glu Ser Lys Asn Lys His Gly  
 260 265 270  
 Leu Thr Pro Leu Leu Leu Gly Val His Glu Gln Lys Gln Gln Val Val  
 275 280 285  
 Lys Phe Leu Ile Lys Lys Lys Ala Asn Leu Asn Ala Leu Asp Arg Tyr  
 290 295 300  
 Gly Arg Thr Ala Leu Ile Leu Ala Val Cys Cys Gly Ser Ala Ser Ile  
 305 310 315 320  
 Val Ser Leu Leu Leu Glu Gln Asn Ile Asp Val Ser Ser Gln Asp Leu  
 325 330 335  
 Ser Gly Gln Thr Ala Arg Glu Tyr Ala Val Ser Ser His His Val  
 340 345 350  
 Ile Cys Gln Leu Leu Ser Asp Tyr Lys Glu Lys Gln Met Leu Lys Ile



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      355      360      365
Ser Ser Glu Asn Ser Asn Pro Glu Gln Asp Leu Lys Leu Thr Ser Glu
  370      375      380
Glu Glu Ser Gln Arg Phe Lys Gly Ser Glu Asn Ser Gln Pro Glu Lys
  385      390      395      400
Met Ser Gln Glu Pro Glu Ile Asn Lys Asp Gly Asp Arg Glu Val Glu
      405      410      415
Glu Glu Met Lys Lys His Glu Ser Asn Asn Val Gly Leu Leu Glu Asn
      420      425      430
Leu Thr Asn Gly Val Thr Ala Gly Asn Gly Asp Asn Gly Leu Ile Pro
      435      440      445
Gln Arg Lys Ser Arg Thr Pro Glu Asn Gln Gln Phe Pro Asp Asn Glu
      450      455      460
Ser Glu Glu Tyr His Arg Ile Cys Glu Leu Val Ser Asp Tyr Lys Glu
  465      470      475      480
Lys Gln Met Pro Lys Tyr Ser Ser Glu Asn Ser Asn Pro Glu Gln Asp
      485      490      495
Leu Lys Leu Thr Ser Glu Glu Glu Ser Gln Arg Leu Glu Gly Ser Glu
      500      505      510
Asn Gly Gln Pro Glu Leu Glu Asn Phe Met Ala Ile Glu Glu Met Lys
      515      520      525
Lys His Gly Ser Thr His Val Gly Phe Pro Glu Asn Leu Thr Asn Gly
      530      535      540
Ala Thr Ala Gly Asn Gly Asp Asp Gly Leu Ile Pro Pro Arg Lys Ser
  545      550      555      560
Arg Thr Pro Glu Ser Gln Gln Phe Pro Asp Thr Glu Asn Glu Glu Tyr
      565      570      575
His Ser Asp Glu Gln Asn Asp Thr Gln Lys Gln Phe Cys Glu Glu Gln
      580      585      590
Asn Thr Gly Ile Leu His Asp Glu Ile Leu Ile His Glu Glu Lys Gln
      595      600      605
Ile Glu Val Val Glu Lys Met Asn Ser Glu Leu Ser Leu Ser Cys Lys
      610      615      620
Lys Glu Lys Asp Ile Leu His Glu Asn Ser Thr Leu Arg Glu Glu Ile
  625      630      635      640
Ala Met Leu Arg Leu Glu Leu Asp Thr Met Lys His Gln Ser Gln Leu
      645      650      655

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&lt;210&gt; 380

&lt;211&gt; 671

&lt;212&gt; PRT

&lt;213&gt; Homo sapien

&lt;400&gt; 380

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Met Val Val Glu Val Asp Ser Met Pro Ala Ala Ser Ser Val Lys Lys
  1      5      10      15
Pro Phe Gly Leu Arg Ser Lys Met Gly Lys Trp Cys Cys Arg Cys Phe
      20      25      30
Pro Cys Cys Arg Glu Ser Gly Lys Ser Asn Val Gly Thr Ser Gly Asp
      35      40      45
His Asp Asp Ser Ala Met Lys Thr Leu Arg Ser Lys Met Gly Lys Trp
      50      55      60
Cys Arg His Cys Phe Pro Cys Cys Arg Gly Ser Gly Lys Ser Asn Val
  65      70      75      80
Gly Ala Ser Gly Asp His Asp Asp Ser Ala Met Lys Thr Leu Arg Asn
      85      90      95
Lys Met Gly Lys Trp Cys Cys His Cys Phe Pro Cys Cys Arg Gly Ser
      100      105      110

```

Gly	Lys	Ser	Lys	Val	Gly	Ala	Trp	Gly	Asp	Tyr	Asp	Asp	Ser	Ala	Phe
		115					120					125			
Met	Glu	Pro	Arg	Tyr	His	Val	Arg	Gly	Glu	Asp	Leu	Asp	Lys	Leu	His
	130					135					140				
Arg	Ala	Ala	Trp	Trp	Gly	Lys	Val	Pro	Arg	Lys	Asp	Leu	Ile	Val	Met
145					150					155					160
Leu	Arg	Asp	Thr	Asp	Val	Asn	Lys	Lys	Asp	Lys	Gln	Lys	Arg	Thr	Ala
			165						170					175	
Leu	His	Leu	Ala	Ser	Ala	Asn	Gly	Asn	Ser	Glu	Val	Val	Lys	Leu	Leu
		180						185					190		
Leu	Asp	Arg	Arg	Cys	Gln	Leu	Asn	Val	Leu	Asp	Asn	Lys	Lys	Arg	Thr
	195						200					205			
Ala	Leu	Ile	Lys	Ala	Val	Gln	Cys	Gln	Glu	Asp	Glu	Cys	Ala	Leu	Met
	210					215					220				
Leu	Leu	Glu	His	Gly	Thr	Asp	Pro	Asn	Ile	Pro	Asp	Glu	Tyr	Gly	Asn
225					230					235					240
Thr	Thr	Leu	His	Tyr	Ala	Ile	Tyr	Asn	Glu	Asp	Lys	Leu	Met	Ala	Lys
			245					250						255	
Ala	Leu	Leu	Leu	Tyr	Gly	Ala	Asp	Ile	Glu	Ser	Lys	Asn	Lys	His	Gly
		260					265						270		
Leu	Thr	Pro	Leu	Leu	Leu	Gly	Val	His	Glu	Gln	Lys	Gln	Gln	Val	Val
	275						280					285			
Lys	Phe	Leu	Ile	Lys	Lys	Lys	Ala	Asn	Leu	Asn	Ala	Leu	Asp	Arg	Tyr
	290				295						300				
Gly	Arg	Thr	Ala	Leu	Ile	Leu	Ala	Val	Cys	Cys	Gly	Ser	Ala	Ser	Ile
305					310					315					320
Val	Ser	Leu	Leu	Leu	Glu	Gln	Asn	Ile	Asp	Val	Ser	Ser	Gln	Asp	Leu
			325					330						335	
Ser	Gly	Gln	Thr	Ala	Arg	Glu	Tyr	Ala	Val	Ser	Ser	His	His	His	Val
			340					345					350		
Ile	Cys	Gln	Leu	Leu	Ser	Asp	Tyr	Lys	Glu	Lys	Gln	Met	Leu	Lys	Ile
	355						360					365			
Ser	Ser	Glu	Asn	Ser	Asn	Pro	Glu	Gln	Asp	Leu	Lys	Leu	Thr	Ser	Glu
	370				375						380				
Glu	Glu	Ser	Gln	Arg	Phe	Lys	Gly	Ser	Glu	Asn	Ser	Gln	Pro	Glu	Lys
385					390					395					400
Met	Ser	Gln	Glu	Pro	Glu	Ile	Asn	Lys	Asp	Gly	Asp	Arg	Glu	Val	Glu
			405						410					415	
Glu	Glu	Met	Lys	Lys	His	Glu	Ser	Asn	Asn	Val	Gly	Leu	Leu	Glu	Asn
		420						425					430		
Leu	Thr	Asn	Gly	Val	Thr	Ala	Gly	Asn	Gly	Asp	Asn	Gly	Leu	Ile	Pro
	435						440					445			
Gln	Arg	Lys	Ser	Arg	Thr	Pro	Glu	Asn	Gln	Gln	Phe	Pro	Asp	Asn	Glu
	450					455					460				
Ser	Glu	Glu	Tyr	His	Arg	Ile	Cys	Glu	Leu	Val	Ser	Asp	Tyr	Lys	Glu
465					470					475					480
Lys	Gln	Met	Pro	Lys	Tyr	Ser	Ser	Glu	Asn	Ser	Asn	Pro	Glu	Gln	Asp
			485						490					495	
Leu	Lys	Leu	Thr	Ser	Glu	Glu	Glu	Ser	Gln	Arg	Leu	Glu	Gly	Ser	Glu
		500						505					510		
Asn	Gly	Gln	Pro	Glu	Lys	Arg	Ser	Gln	Glu	Pro	Glu	Ile	Asn	Lys	Asp
	515						520					525			
Gly	Asp	Arg	Glu	Leu	Glu	Asn	Phe	Met	Ala	Ile	Glu	Glu	Met	Lys	Lys
	530					535					540				
His	Gly	Ser	Thr	His	Val	Gly	Phe	Pro	Glu	Asn	Leu	Thr	Asn	Gly	Ala
545					550					555					560
Thr	Ala	Gly	Asn	Gly	Asp	Asp	Gly	Leu	Ile	Pro	Pro	Arg	Lys	Ser	Arg
			565						570						575

Thr Pro Glu Ser Gln Gln Phe Pro Asp Thr Glu Asn Glu Glu Tyr His  
 580 585 590  
 Ser Asp Glu Gln Asn Asp Thr Gln Lys Gln Phe Cys Glu Glu Gln Asn  
 595 600 605  
 Thr Gly Ile Leu His Asp Glu Ile Leu Ile His Glu Glu Lys Gln Ile  
 610 615 620  
 Glu Val Val Glu Lys Met Asn Ser Glu Leu Ser Leu Ser Cys Lys Lys  
 625 630 635 640  
 Glu Lys Asp Ile Leu His Glu Asn Ser Thr Leu Arg Glu Glu Ile Ala  
 645 650 655  
 Met Leu Arg Leu Glu Leu Asp Thr Met Lys His Gln Ser Gln Leu  
 660 665 670

<210> 381  
 <211> 251  
 <212> DNA  
 <213> Homo sapien

<400> 381  
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 ggtaacatgc ttcccctaag ggtatcccaa cccaggggcc tcaccatgac ctctgagggg 120  
 ccaatatccc aggagaagca ttggggaggt gggggcaggt gaaggacca ggactcacac 180  
 atcctggggc tccaaggcag aggagagggt cctcaagaag gtcaggagga aaatccgtaa 240  
 caagcagtca g 251

<210> 382  
 <211> 3279  
 <212> DNA  
 <213> Homo sapiens

<400> 382  
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 cactgggagg ggacatcctg cagaaggtag gagttagcaa acacccgctg caggggaggg 180  
 gagagccctg cggcacctgg gggagcagag ggagcagcac ctgcccaggc ctgggaggag 240  
 gggcctggag ggcgtgagga ggagcgagg ggcgtcatgg ctggagttag ggatcagggg 300  
 cagggcgaga gatggcctca cacagggaag agaggggccc tctgcaggg cctcacctgg 360  
 gccacaggag gacactgctt ttctctgag gagttaggag ctgtggatgg tgcaggacag 420  
 aagaaggaca gggcctggct caggtgtcca gaggtgtcg ctggcttccc tttgggatca 480  
 gactgcaggg agggagggcg gcagggttgt ggggggagtg acgatgagga tgacctgggg 540  
 gtggctccag gccttgcccc tgccctgggc ctaccccagc ctccctcaca gtctcctggc 600  
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 gaactgacca taccagccc tgcccacggc cctccatggc tccccaatgc cctggagagg 720  
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 ggaccttgcc ccttgtgcag gagctggacc ctgaagtccc ctcccatag gccaaagactg 900  
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 catttctgtc tgttctctgag agctgggaat tgcctcagc catctgcctg cgcggttctg 1020  
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 ttacccttag ggtgattctg ggggtccact tgtctgtaat ggtgtgcttc aaggtatcac 1140  
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 gacctgtgct ttctggtgtg gactccaggg ctgctaggaa aaggaatggg cagacacagg 1440  
 tgtatgcaa tgtttctgaa atgggtataa ttctgtcctc tcttctggaa cactggctgt 1500  
 ctctgaagac ttctcgtcca gtttcagtga ggcacacac aaagacgtgg gtgacctgt 1560  
 tgtttgtggg gtgcagagat gggaggggtg gggccacccc tggaagagtg gacagtgaca 1620

```

caaggtggac actctctaca gatcactgag gataagctgg agccacaatg catgaggcac 1680
acacacagca aggttgacgc tgtaaacata gccacgctg tcctgggggc actgggaagc 1740
ctagataagg ccgtgagcag aaagaagggg aggatccctc tatgttggtg aaggaggac 1800
tagggggaga aactgaaagc tgattaatta caggagggtt gttcagggtc cccaaaccac 1860
cgtcagatgtt gatgatttcc tagcaggact tacagaaata aagagctatc atgctgtggt 1920
ttattatggt ttgttacatt gataggatac atactgaaat cagcaaacia aacagatgta 1980
tagattagag tgtggagaaa acagaggaaa acttgaggtt acgaagactg gcaacttggc 2040
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gtgtccagggt tttttactgg ggggtctgtg gacgagtatg gactactga ataattgacc 2340
tgaagtcctc agacctgagg ttccctagag ttcaaacaga tacagcatgg tccagagtcc 2400
cagatgtaca aaaacagggg ttcatcacia atcccattct tagcatgaag ggtctggcat 2460
ggccaagggc cccaagtata tcaaggcact tgggcagaac atgccaagga atcaaatgtc 2520
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atcattgttt tatttgcctt cttttcacac cattggtgag ggagggatta ccacctggg 2820
gttatgaaga tgggtgaaca cccacacat agcaccggag atatgagatc aacagtctt 2880
tagccataga gattcacagc ccagagcagg aggacgtgc acaccatgca ggatgacatg 2940
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acaagacggg ggggcaaact ctgatttccg tgggggaatg tcatggtctt gctttactaa 3060
gttttgagac tggcaggtag tgaaactcat taggctgaga acctgttgga atgcagctga 3120
cccagctgat agaggaagta gccaggtggg agcctttccc agtgggtgtg ggacatatct 3180
ggcaagatgt tgtggcactc ctggttacag atactggggc agcaaataaa actgaatctt 3240
gttttcagac cttaaaaaaa aaaaaaaaaa aaaagtgtt 3279

```

&lt;210&gt; 383

&lt;211&gt; 154

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 383

```

Met Ala Gly Val Arg Asp Gln Gly Gln Gly Ala Arg Trp Pro His Thr
      5                      10                      15

Gly Lys Arg Gly Pro Leu Leu Gln Gly Leu Thr Trp Ala Thr Gly Gly
      20                      25                      30

His Cys Phe Ser Ser Glu Glu Ser Gly Ala Val Asp Gly Ala Gly Gln
      35                      40                      45

Lys Lys Asp Arg Ala Trp Leu Arg Cys Pro Glu Ala Val Ala Gly Phe
      50                      55                      60

Pro Leu Gly Ser Asp Cys Arg Glu Gly Gly Arg Gln Gly Cys Gly Gly
      65                      70                      75                      80

Ser Asp Asp Glu Asp Asp Leu Gly Val Ala Pro Gly Leu Ala Pro Ala
      85                      90                      95

Trp Ala Leu Thr Gln Pro Pro Ser Gln Ser Pro Gly Pro Gln Ser Leu
      100                     105                     110

Pro Ser Thr Pro Ser Ser Ile Trp Pro Gln Trp Val Ile Leu Ile Thr
      115                     120                     125

```

Glu Leu Thr Ile Pro Ser Pro Ala His Gly Pro Pro Trp Leu Pro Asn  
 130 135 140

Ala Leu Glu Arg Gly His Leu Val Arg Glu  
 145 150

<210> 384

<211> 557

<212> DNA

<213> Homo sapiens

<400> 384

```

ggatcctcta gagcgccgc ctactactac taaattcgcg gccgcgtcga cgaagaagag 60
aaagatgtgt ttgttttgg actctctgtg gtcccttcca atgctgtggg ttccaacca 120
ggggaagggt cccttttgca ttgccaagtg ccataaccat gagcactact ctaccatggt 180
tctgcctcct ggccaagcag gctggtttgc aagaatgaaa tgaatgattc tacagctagg 240
acttaacctt gaaatggaaa gtcttgcaat cccatttgca ggatccgtct gtgcacatgc 300
ctctgtagag agcagcattc ccagggaacct tggaaacagt tggcactgta aggtgcttgc 360
tccccaagac acatcctaaa aggtgttgta atggtgaaaa cgtcttcctt ctttattgcc 420
ccttcttatt tatgtgaaca actgtttgtc tttttttgta tcttttttaa actglaaagt 480
tcaattgtga aaatgaatat catgcaaata aattatgcga ttttttttcc aaagtaaaaa 540
aaaaaaaaaa aaaaaaa 557

```

<210> 385

<211> 337

<212> DNA

<213> Homo sapiens

<400> 385

```

ttcccagggtg atgtgcgagg gaagacacat ttactatcct tgatgggggt gattccttta 60
gtttctctag cagcagatgg gttaggagga agtgacccaa gtggttgact cctatgtgca 120
tttcaaagcc atctgctgtc ttcgagtagc gacacatcat cactcctgca ttgttgatca 180
aaacgtggag gtgcttttcc tcagctaaga agcccttagc aaaagctcga atagacttag 240
tatcagacag gtccagtttc cgcaccaaca cctgctggtt ccctgtcgtg gtctggatct 300
ctttggccac caattccccc ttttccacat ccggca 337

```

<210> 386

<211> 300

<212> DNA

<213> Homo sapiens

<400> 386

```

gggcccgtcta cgggccagg ccccgccctcg cgagtectcc tccccgggtg cctgcccgca 60
gccgcgtcgg ccagaggggt gggcgcgggg ctgcctctac cggctggcgg ctgtaactca 120
gggaccttgg ccgaagggt ctagcaagga cccaccgacc ccagccgcgg cggcggcggc 180
gggactttg ccggtgtgt gggcgggagc ggactgcgtg tccgcggacg ggcagcgaag 240
atgttagcct tcgtgccag gaccgtggac cgatcccagg gctgtggtgt aacctcagcc 300

```

<210> 387

<211> 537

<212> DNA

<213> Homo sapiens

<400> 387

```

gggccgagtc gggcaccaag ggactctttg caggcttcct tctcggatc atcaaggctg 60
ccccctcctg tgccatcatg atcagcacct atgagttcgg caaaagcttc ttccagaggc 120

```

```

tgaaccagga cccggttctg ggcggtgaa aggggcaagg aggcaaggac cccgtctctc 180
ccacggatgg ggagagggca ggaggagacc cagccaagtg ccttttctc agcactgagg 240
gagggggctt gtttcccttc cctcccgccg acaagctcca gggcagggtt gtcctctctg 300
gcggccacgc acttctctcag acacaacttc ttctgtctgc tccagtctgt gggatcatca 360
cttaccacc ccccaagttc aagaccaaatt cttccagctg ccccttctgt gtttccctgt 420
gtttgtctga gctgggcatg tctccaggaa ccaagaagcc ctccagctgg tgtagtctcc 480
ctgacccttg ttaattcctt aagtctaaag atgatgaact tcaaaaaaaaa aaaaaaa 537

```

&lt;210&gt; 388

&lt;211&gt; 520

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 388

```

aggataatTT ttaaaccaat caaatgaaaa aaacaaacaa acaaaaaagg aaatgtcatg 60
tgaggTTaaa ccagtttgca ttcccctaatt gtggaaaaag taagaggact actcagcact 120
gtttgaagat tgctcttctt acagcttctg agaattgtgt tatttcactt gccaaagtga 180
ggacccctc cccaacatgc ccagcccac ccctaagcat ggtcccttgt caccaggcaa 240
ccaggaaact gctacttgtg gacctacca gagaccagga gggtttggtt agctcacagg 300
acttccccca cccagaaga ttagcatccc atactagact cataactcaac tcaactaggc 360
tcatactcaa ttgatggTTa ttagacaatt ccatttcttt ctggTTatta taaacagaaa 420
atctttctc ttctcattac cagtaaaggc tcttggtatc tttctgttgg aatgatttct 480
atgaacttgt cttattTTaa tggTgggttt tttttctggt 520

```

&lt;210&gt; 389

&lt;211&gt; 365

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 389

```

cgTTgcccc gtttgacaga aggaaaggcg gagcttattc aaagtctaga gggagtggag 60
gagTTaaggc tggatttcag atctgcctgg ttccagccgc agtTgcccT ctgctcccc 120
aacgactttc caaataatct caccagcgcc ttccagctca ggcTccTag aagcgtcttg 180
aagcctatgg ccagctgtct ttgtgttccc tctcaccgc ctgTccTcac agctgagact 240
cccaggaaac cttcagacta ccttctctg ccttcagcaa gggcgTtgC ccacattctc 300
tgagggtcag tggaagaacc tagactccca ttgctagagg tagaaagggg aagggtgctg 360
gggag 365

```

&lt;210&gt; 390

&lt;211&gt; 221

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; (1)...(221)

&lt;223&gt; n = A,T,C or G

&lt;400&gt; 390

```

tgctctcca tcttgcccc gacttctctg tcaggaaagt ggggatggac cccatctgca 60
tacacggnTT ctcatgggtg tggaacatct ctgcttgccg tttcaggaag gcctctggct 120
gctctangag tctgancnga ntcgttgccc cantntgaca naaggaaagg cggagcttat 180
tcaaagtcta gagggagtgg aggagttaag gctggatttc a 221

```

&lt;210&gt; 391

&lt;211&gt; 325

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; (1)...(325)

&lt;223&gt; n = A,T,C or G

&lt;400&gt; 391

```

tggagcaggt cccgaggcct cccctagagcc tggggcccgac tctgtgncga tgcangcttt 60
ctctcgcgcc cagcctggag ctgctcctgg catctaccaa caatcagncg aggcgagcag 120
tagccagggc actgctgcc aacagccagtc cnnataccat catgtnaccc ggtgngctct 180
naanttingat ntccanagcc ctaccccaten tagttctgct ctcccaccgg ntaccagccc 240
cactgcccag gaatcctaca gccagtaccc tgtcccgcag tctctaccta ccagtacgat 300
gagacctccg gctactacta tgacc                                     325

```

&lt;210&gt; 392

&lt;211&gt; 277

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; (1)...(277)

&lt;223&gt; n = A,T,C or G

&lt;400&gt; 392

```

atattgttta actccctcct ttatatcttt taacattttc atggngaaag gttcacatct 60
agtctcactt nqgcagngn ctccacttg agtctcttcc ccggcctggn ccagtngnaa 120
antaccanga accgncatgn cttanaaen nccctggtttn tgggttnntc aatgactgca 180
tgcagtgcac caccctgtcc actacgtgat gctgtaggat taaagtctca cagtgggcgg 240
ctgaggatag agcgcgcgt cctgtgttgc tggggaa                                     277

```

&lt;210&gt; 393

&lt;211&gt; 566

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 393

```

actagtcag tgtgggtggaa ttgcgggccg cgtcgacgga caggtcagct gtctggctca 60
gtgatctaca ttctgaagtt gtctgaaaat gtcttcatga ttaaattcag cctaaacggt 120
ttgccgggaa cactgcagag acaatgctgt gagtttccaa ccttagccca tctgcgggca 180
gagaaggctct agtttgtcca tcagcattat catgatatca ggactgggta cttgggtaag 240
gaggggtcta ggagatctgt cccctttaga gacaccttac ttataatgaa gtatttggga 300
gggtgggttt caaaagtaga aatgtcctgt attccgatga tcatcctgta aacattttat 360
catttattaa tcacccctgc ctgtgtctat tattatattc atatctctac gctggaaact 420
ttctgcctca atgtttactg tgcctttgtt ttgtctagtt tgtgtgttg aaaaaaaaaa 480
cattctctgc ctgagtttta atttttgtcc aaagtatttt taatctatac aattaaaagc 540
ttttgcctat caaaaaaaaaa aaaaaa                                     566

```

&lt;210&gt; 394

&lt;211&gt; 384

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; (1)...(384)

&lt;223&gt; n = A,T,C or G

<400> 394  
 gaacatacat gtcccgggcac ctgagctgca gtctgacatc atcgccatca cgggcctcgc 60  
 tgcaaatng gaccggggcca aggcctggact gctggagcgt gtgaaggagc tacaggccna 120  
 gcaggaggac cgggcttttaa ggagtttttaa gctgagtgtc actgtagacc ccaaatacca 180  
 tcccaagatt atcgggagaa agggggcagt aattacccaa atccggttgg agcatgacgt 240  
**gaacatccag tttcctgata aggacgatgg gaaccagccc caggacccaa ttaccatcac** 300  
 aggttacgaa aagaacacag aagctgccag ggatgctata ctgagaattg tgggtgaact 360  
 tgagcagatg gtttctgagg acgt 384

<210> 395  
 <211> 399  
 <212> DNA  
 <213> Homo sapiens

<400> 395  
 ggcaaaactg tgtgacctca ataagacctc gcagatccaa ggtcaagtat cagaagtgc 60  
 tctgaccttg gactccaaga cctacatcaa cagcctggct atattagatg atgagccagt 120  
 tatcagaggt ttcattcatt cggaattgt ggagtctaag gaaatcatgg cctctgaagt 180  
 attcacgtct ttccagtacc ctgagttctc tatagagttg cctaacacag gcagaattgg 240  
 ccagctactt gtctgcaatt gtatcttcaa gaataccctg gccatccctt tgactgacgt 300  
 caagttctct ttggaaagcc tgggcatctc ctactacag acctctgacc atgggacggt 360  
 gcagcctggg gagaccatcc aatcccaaat aaaatgcac 399

<210> 396  
 <211> 403  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> misc\_feature  
 <222> (1)...(403)  
 <223> n = A,T,C or G

<400> 396  
 tggagtntc agtgcaaaca agccataaag cttcagtagc aaattactgt ctcacagaaa 60  
 gacattttca acttctgctc cagctgctga taaaacaaat catgtgttta gcttgactcc 120  
 agacaaggac aacctgttcc ttcataactc tctagagaaa aaaaggagtt gttagtagat 180  
 actaaaaaaa gtggatgaat aatctggata tttttcctaa aaagattcct tgaaacacat 240  
 taggaaaatg gagggccta tgatcagaat gctagaatta gtccattgtg ctgaagcagg 300  
 gtttagggga gggagtgagg gataaaagaa ggaaaaaaag aagagtgaga aaacctattt 360  
 atcaaagcag gtgctatcac tcaatgttag gccctgctct ttt 403

<210> 397  
 <211> 100  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> misc\_feature  
 <222> (1)...(100)  
 <223> n = A,T,C or G

<400> 397  
 actagtnacg tgtgggtggaa ttccggggccg cgtcgacctc naanccatct ctatagcaaa 60  
 tccatccccg ctcttggttg gtnacagaat gactgacaaa 100

<210> 398  
 <211> 278



<212> DNA  
 <213> Homo sapiens

<220>  
 <221> misc\_feature  
 <222> (1)...(278)  
 <223> n = A,T,C or G

<400> 398  
 ggggcccgcgt cgacagcagt tccgccagcg ctcccccctg ggtggggatg tgctgcacgc 60  
 ccacctggac atctggaagt cagcggcctg gatgaaagag cggacttcac ctggggcgat 120  
 tcaactactgt gcctcgacca gtgaggagag ctggaccgac agcgaggtgg actcatcatg 180  
 ctccgggcag cccatccacc tgtggcagtt cctcaaggag ttgctactca agccccacag 240  
 ctatggccgc ttcattangt ggctcaacaa ggagaagg 278

<210> 399  
 <211> 298  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> misc\_feature  
 <222> (1)...(298)  
 <223> n = A,T,C or G

<400> 399  
 acggaggtgg aggaagcgnc cctgggatcg anaggatggg tcctgncatt gaccnccctn 60  
 ggggtgccng catggagcgc atgggcgcgg gcctgggcca cggcatggat cgcgtgggct 120  
 ccgagatcga gcgcattggc ctggatcatgg accgcatggg ctccgtggag cgcattgggct 180  
 ccggcattga gcgcattggc ccgctgggcc tcgaccacat ggccctccanc attgancgca 240  
 tgggccagac catggagcgc attggctctg gcgtggagcn catgggtgcc ggcatggg 298

<210> 400  
 <211> 548  
 <212> DNA  
 <213> Homo sapiens

<400> 400  
 acatcaacta cttcctcatt ttaaggatat gcagttccct tcctcccctt ttctgcctt 60  
 gtacatgtac atgtatgaaa ttcccttctc ttaccgaact ctctccacac atcacaagggt 120  
 caaagaacca cacgcttaga agggtaagag ggcaccctat gaaatgaaat ggtgatttct 180  
 tgagtctctt ttttccacgt ttaaggggcc atggcaggac ttagagttgc gagttaagac 240  
 tgcagagggc tagagaatta ttccatacag gctttgaggc caccatgtc acttatcccg 300  
 tataccctct caccatcccc ttgtctactc tgatgcccc aagatgcaac tgggcagcta 360  
 gttggcccca taattctggg cctttgttgt ttgttttaat tacttgggca tcccaggaag 420  
 ctttccagtg atctcctacc atgggcccc ctccgtggat caagcccctc ccaggccctg 480  
 tccccagccc ctccgtcccc agcccacccg cttgccttgg tgctcagccc tcccattggg 540  
 agcaggtt 548

<210> 401  
 <211> 355  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> misc\_feature  
 <222> (1)...(355)  
 <223> n = A,T,C or G

<400> 401  
actgttttcca tgttatgttt ctacacattg ctacctcagt gctcctggaa acttagcttt 60  
tgatgtctcc aagtagtcca ctttcattta actctttgaa actgtatcat ctttgccaag 120  
taagagtggg ggcctatttc agctgctttg acaaaatgac tggctcctga cttaacgttc 180  
tataaatgaa tgtgctgaag caaagtgcc atggtggcgg cgaagaagan aaagatgtgt 240  
tttgttttgg actctctgtg gtcccttcca atgctgnggg tttccaacca ggggaagggt 300  
cccttttgca ttgccaagtg ccataacctat gaggactact ctaccatggn tctgc 355

<210> 402  
<211> 407  
<212> DNA  
<213> Homo sapiens

<220>  
<221> misc\_feature  
<222> (1)...(407)  
<223> n = A,T,C or G

<400> 402  
atgggggcaag ctggataaag aaccaagacc cactggagta tgctgtcttc aagaaaccca 60  
tctcacatgc ggtggcatat ataggctcaa aataaaggaa tggagaaaaa tatttcaagc 120  
aatggaaaaa cagaaaaaag caggtgttgc actcctactt tctgacaaaa cagactatgc 180  
gaataaagat aaaaaagaga aggacattac aaaggtggtc ctgacctttg ataaatctca 240  
ttgcttgata ccaacctggg ctgttttaat tgcccaaacc aaaaggataa tttgctgagg 300  
ttgtggagct tctccctgc agagagtccc tgatctcca aaatttggtt gagatgtaag 360  
gntgattttg ctgacaactc ctttctgaa gttttactca tttccaa 407

<210> 403  
<211> 303  
<212> DNA  
<213> Homo sapiens

<220>  
<221> misc\_feature  
<222> (1)...(303)  
<223> n = A,T,C or G

<400> 403  
cagtatttat agcnaactg aaaagctagt agcaggcaag tctcaaatcc aggcacccaa 60  
tctaagcaa gagccatggc atggtgaaaa tgcaaaagga gagtctggcc aatctacaaa 120  
tagagaacaa gacctactca gtcataaaca aaaaggcaga caccaacatg gatctcatgg 180  
gggattggat attgtaatta tagagcagga agatgacagt gatcgtcatt tggcacaaca 240  
tcttaacaac gaccgaaacc cattatttac ataaacctcc attcggtaac catgttgaaa 300  
gga 303

<210> 404  
<211> 225  
<212> DNA  
<213> Homo sapiens

<400> 404  
aagtgttaact tttaaaaatt tagtggattt tgaaaattct tagaggaaag taaaggaaaa 60  
attgttaatg cactcattta cttttacatg gtgaaagtto tctcttgato ctacaaacag 120  
acattttcca ctctgttttc catagtgtgt aagtgtatca gatgtgttgg gcatgtgaat 180  
ctccaagtgc ctgtgtaata aataaagtat ctttatttca ttcatt 225

<210> 405

<111> 334  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> misc\_feature  
 <222> (1)...(334)  
 <223> n = A,T,C or G

<400> 405  
 gactgtgttat actgtgagtt ctactaggaa atcatcaaat ctgaggggttg tctggaggac 60  
 ctcaatacac ctccccccat agtgaatcag ctccaggagg gtccagtcac tctccttact 120  
 tcatccccat cccatgccaa aggaagaccc tccctccttg gctcacagcc ttctctaggc 180  
 ctccagtgcc ctccaggaca gagtgggtta tgttttcagc tccatccttg ctgtgagtggt 240  
 ctgggtgcggg tgtgcctcca gcttctgctc agtgcttcat ggacagtgtc cagcccatgt 300  
 cactctccac tctctcanng tggatccac ccct 334

<210> 406  
 <211> 216  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> misc\_feature  
 <222> (1)...(216)  
 <223> n = A,T,C or G

<400> 406  
 ttctatacct aatgagggag ttganatnac atnnaaccag gaaatgcatg gatctcaang 60  
 gaaacaaaca cccaataaac tcggagtggc agactgacaa ctgtgagaca tgcacttget 120  
 acnaaacaca aatttnatgt tgcacccttg tttctacacc tgtgggttat gacaaagaca 180  
 actgccaaag aatnttcaag aaggaggact gccant 216

<210> 407  
 <211> 413  
 <212> DNA  
 <213> Homo sapiens

<400> 407  
 gctgacttgc tagtatcatc tgcattcatt gaagcacaag aacttcatgc cttgactcat 60  
 gtaaatgcaa taggattaaa aaataaattt gatatcacat ggaaacagac aaaaaatatt 120  
 gtacaacatt gcacccagtg tcagattcta cacctggcca ctgaggaagc aagagttaat 180  
 cccagagggtc tatgtcctaa tgtgttatgg caaatggatg tcatgcacgt accttcattt 240  
 ggaaaattgt catttgtcca tgtgacagtt gatacttatt cacatttcat atgggcaacc 300  
 tgccagacag gagaaagtct tcccatgtta aaagacattt attatcttgt ttctctgtca 360  
 tgggagttcc agaaaaagtt aaaacagaca atggggccagg ttctgtagta aag 413

<210> 408  
 <211> 183  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> misc\_feature  
 <222> (1)...(183)  
 <223> n = A,T,C or G

<400> 408

```

ggagctngcc ctcaattcct ccatntctat gttancatat ttaatgtctt ttgnnattaa 60
tnccttaacta gttaatcctt aaagggctan ntaatcctta actagtcctt ccattgtgag 120
cattatcctt ccagtattcn ccttctnttt tatttactcc ttcttggtta cccatgtact 180
ntt                                     183

```

<210> 409

<211> 250

<212> DNA

<213> Homo sapiens

<220>

<221> misc\_feature

<222> (1)...(250)

<223> n = A,T,C or G

<400> 409

```

cccacgcatg ataagctctt tttttctgta agtcctgcta ggaaatcatc aaatctgacg 60
gtgggtttggg ggacctgaac aaacctcctg taattaatca gctttcagtt tctcccccta 120
gtccctcctt caacaacata ggaggatcct ccccttcttt ctgtcacagg ccttatctag 180
gcttcccagt gccccagga cagcgtgggc tatgtttaca gcgctcctt gctggggggg 240
ggcctatgc                                     250

```

<210> 410

<211> 306

<212> DNA

<213> Homo sapiens

<220>

<221> misc\_feature

<222> (1)...(306)

<223> n = A,T,C or G

<400> 410

```

ggctgggttg caagaatgaa atgaatgatt ctacagctag gacttaacct tgaaatggaa 60
agtcttgcaa tccattttgc aggatccgtc tgtgcacatg cctctgtaga gagcagcatt 120
cccagggaacc ttggaaacag ttggcactgt aagggtgcttg ctccccaaga cacatcctaa 180
aagggtgttg aatggtgaaa accgcttcct tctttattgc ccttcttat ttatgtgaac 240
nactgggttg ctttttttgn atcttttta aactggaaag ttcaattgng aaaatgaata 300
tentgc                                     306

```

<210> 411

<211> 261

<212> DNA

<213> Homo sapiens

<220>

<221> misc\_feature

<222> (1)...(261)

<223> n = A,T,C or G

<400> 411

```

agagatattt cttaggtnaa agttcataga gttcccatga actatatgac tggccacaca 60
ggatcttttg tatttaagga ttctgagatt ttgcttgagc aggattagat aaggctgttc 120
tttaaatgtc tgaaatggaa cagatttcaa aaaaaaaccc cacaatctag ggtgggaaca 180
aggaaggaaa gatgtgaata ggctgatggg caaaaaacca atttaccat cagttccagc 240
cttctctcaa ggngaggcaa a                                     261

```

<210> 412

<211> 241  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> misc\_feature  
 <222> (1)...(241)  
 <223> n = A,T,C or G

<400> 412  
 gtccaatggt acctgacatt tctacaacac ccactcacc gatgtattcg ttgccagtg 60  
 ggaacatacc agcctgaatt tggaaaaaat aattgtgttt cttgccagc aaatactacg 120  
 actgactttg atggctccac aaacataacc cagtgtaaaa acagaagatg tggaggggag 180  
 ctgggagatt tcaactggga cattgaattc ccaaactacc cangcaatta ccagccaac 240  
 a 241

<210> 413  
 <211> 231  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> misc\_feature  
 <222> (1)...(231)  
 <223> n = A,T,C or G

<400> 413  
 aactcttaca atccaagtga ctcatctgtg tgcttgaatc cttccactg tctcatctcc 60  
 ctcatccaag tttctagtac cttctctttg ttgtgaagga taatcaaact gaacaacaaa 120  
 aagtttactc tctcatcttg gaacctaaaa actctcttct tctgggtct gagggctcca 180  
 agaatccttg aatcanttct cagatcattg gggacaccan atcaggaacc t 231

<210> 414  
 <211> 234  
 <212> DNA  
 <213> Homo sapiens

<400> 414  
 actgtccatg aagcactgag cagaagctgg aggcacaacg caccagacac tcacagcaag 60  
 gatggagctg aaaacataac ccactctgtc ctggaggcac tgggaagcct agagaaggct 120  
 gtgagccaag gagggagggt cttccttttg catgggatgg ggatgaagta aggagagggg 180  
 ctggaccccc tggaaactga ttcactatgg ggggaggtgt attgaagtcc tcca 234

<210> 415  
 <211> 217  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> misc\_feature  
 <222> (1)...(217)  
 <223> n = A,T,C or G

<400> 415  
 gcataggatt aagactgagt atcttttcta cattctttta acttttctaag gggcacttct 60  
 caaaacacag accaggtagc aaatctccac tgccttaagg ntctcaccac cactttctca 120  
 cacctagcaa tagtagaatt cagtcctact tctgaggcca gaagaatggg tcagaaaaat 180  
 antggattat aaaaaataac aattaagaaa aataatc 217

<210> 416  
 <211> 213  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> misc\_feature  
 <222> (1)...(213)  
 <223> n = A,T,C or G

<400> 416  
 atgcataatnt aaagganact gcctcgcttt tagaagacat ctggncctgct ctctgcatga 60  
 ggcacagcag taaagctctt tgattcccgag aatcaagaac tctcccttc agactattac 120  
 cgaatgcaag gtgggttaatt gaaggccact aattgatgct caaatagaag gatattgact 180  
 atattggaac agatggagtc tctactacaa aag 213

<210> 417  
 <211> 303  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> misc\_feature  
 <222> (1)...(303)  
 <223> n = A,T,C or G

<400> 417  
 nagtcttcag gcccatcagg gaagttcaca ctggagagaa gtcatacata tgtactgtat 60  
 gtgggaaagg ctttactctg agttcaaata ttcaagccca tcagagagtc cacactggag 120  
 agaagccata caaatgcaat gagtgtggga agagcttcag gagggattcc cattatcaag 180  
 ttcatctagt ggtccacaca ggagagaaac cctataaatg tgagatatgt gggaagggct 240  
 tcantcaaag ttcgtatctt caaatccatc ngaaggncca cagtatanan aaacctttta 300  
 agt 303

<210> 418  
 <211> 328  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> misc\_feature  
 <222> (1)...(328)  
 <223> n = A,T,C or G

<400> 418  
 tttttggcgg tgggtggggca gggacgggac angagtctca ctctgttgcc caggctggag 60  
 tgcacaggca tgatctcggc tcactacaac ccctgcctcc catgtccaag cgattcttgt 120  
 gcctcagcct tcctgttagc tagaattaca ggcacatgcc accacacca gctagttttt 180  
 gtatttttag tagagacagg gtttcacat gttggccagg ctggtctcaa actcctnacc 240  
 tcagnggtca ggctggtctc aaactcctga cctcaagtga tctgcccacc tcagcctccc 300  
 aaagtgctan gattacaggc cgtgagcc 328

<210> 419  
 <211> 389  
 <212> DNA  
 <213> Homo sapiens

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; (1)...(389)

&lt;223&gt; n = A,T,C or G

&lt;400&gt; 419

```

cctcctcaag acggcctgtg gtccgcctcc cggcaaccaa gaagcctgca gtgccatatg 60
cccccctgagc catggactgg agcctgaaaag gcagcgtaca cccctgcctc gatcttgctg 120
cttgtttctc ctctgtggct ccattcatag cacagtgtgt gcactgaggc ttgtgcaggc 180
cgagcaaggc caagctggct caaagagcaa ccagtcaact ctgccacggg gtgccaggca 240
ccggtttctc agccaccaac ctcactcgct cccgcaaata gcacatcagt tcttctaccc 300
caaggttagg accaaagggc atctgctttt ctgaagtctc ctgctctatc agccatcacg 360
tggcagccac tcnggctgtg tcgacgcgg                                     389

```

&lt;210&gt; 420

&lt;211&gt; 408

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 420

```

gttcctccta actcctgcc aaaacagctc tctcaacat gagagctgca cccctcctcc 60
tggccagggc agcaagcctt agccttggct tcttgtttct gcttttttcc tggctagacc 120
gaagtgtact agccaaggag ttgaagtgtg tgactttggt gtttcggcat ggagaccgaa 180
gtccatttga cacccttccc actgacccca taaaggaatc ctcatggcca caaggatttg 240
qccaaactcac ccagctgggc atggagcagc attatgaact tggagagtat ataagaaaaga 300
gatatagaaa attcttgaat gattcctata aacatgaaca gggttatatt cgaagcacag 360
acgttgaccg gactttgatg aagtgcctatg acaaacctgg caagcccg                                     408

```

&lt;210&gt; 421

&lt;211&gt; 352

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; (1)...(352)

&lt;223&gt; n = A,T,C or G

&lt;400&gt; 421

```

gctcaaaaat ctttttactg atnggcattg ctacacaatc attgactatt acggaggcca 60
gaggagaatg aggcctggcc tgggagccct gtgcctacta naagcacatt agattatcca 120
ttcactgaca gaacagggtc tttttgggtc cttcttctcc accacnatac acttgcatgc 180
ctccttcttg aagattcttt ggcagttgtc tttgtcataa cccacagggt tagaaacaag 240
ggtgcaacat gaaatttctg tttcgtagca agtgcatgtc tcacaagttg gcangtctgc 300
cactccgagt ttattgggtg tttgtttcct ttgagatcca tgcatttctc gg                                     352

```

&lt;210&gt; 422

&lt;211&gt; 337

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 422

```

atgccaccat gctggcaatg cagcggggcg tcgaaggcct gcatatccag cccaagctgg 60
cgatgatcga cggcaaccgt tgcccgaagt tgccgatgcc agccgaagcg gtggtcaagg 120
gcgatagcaa ggtgccggcg atcgcgggcg cgtcaatcct ggccaaggtc agccgtgate 180
gtgaaatggc agctgtcgaa ttgatctacc cgggttatgg catcgcgggg cataagggtc 240
atccgacacc ggtgcacctg gaagccttgc agcggctggg gccgacgccg attcaccgac 300
gctttcttcc cgggtacggc tggcctatga aaattat                                     337

```

<210> 423  
 <211> 310  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> misc\_feature  
 <222> (1)...(310)  
 <223> n = A,T,C or G

<400> 423  
 gctcaaaaat ctttttactg atatggcatg gctacacaat cattgactat tagaggccag 60  
 aggagaatga ggcctggcct gggagccctg tgcctactan aagcncatta gattatccat 120  
 tcactgacag aacagggtctt tttgggtcc tcttctcca ccacgatata cttgcagtcc 180  
 tccttcttga agattctttg gcagttgtct ttgtcataac ccacaggtgt anaaacaagg 240  
 gtgcaacatg aaatttctgt ttcgtagcaa gtgcatgtct cacagttgtc aagtctgccc 300  
 tccgagttta 310

<210> 424  
 <211> 370  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> misc\_feature  
 <222> (1)...(370)  
 <223> n = A,T,C or G

<400> 424  
 gctcaaaaat ctttttactg ataggcatgg ctacacaatc attgactatt agaggccaga 60  
 ggagaatgag gcctggcctg ggagccctgt gcctactaga agcacattag attatccatt 120  
 cactgacaga acagggtctt tttgggtcct tcttctccac cacgatatac ttgcagtcct 180  
 ccttcttgaa gattcttttg cagttgtctt tgtcataacc cacaggtgta gaaacatcct 240  
 ggttgaatct cctggaactc cctcattagg tatgaaatag catgatgcat tgcataaagt 300  
 cacgaaggtg gcaaagatca caacgctgcc cagganaaca ttcattgtga taagcaggac 360  
 tccgtcgcagc 370

<210> 425  
 <211> 216  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> misc\_feature  
 <222> (1)...(216)  
 <223> n = A,T,C or G

<400> 425  
 aattgctatn ntttatcttg ccactcaaaa taattaccaa aaaaaaaaaa tnttaaataga 60  
 taacaacnca acatcaaggn aaananaaca ggaatggntg actntgcata aatnggccga 120  
 anattatcca ttatnttaag ggttgacttc aggnacagc acacagacaa acatgcccag 180  
 gaggnnttca ggaccgctcg atgtntntg aggagg 216

<210> 426  
 <211> 596  
 <212> DNA  
 <213> Homo sapiens



```

<400> 426
cttccagtga ggataaccct gttgccccgg gccgaggttc tccattagge tctgattgat 60
tugcagtcag tgatggaagg gtgttctgat cattccgact gcccccaaggg tegtgggcca 120
gctctctgtt ttgctgagtt ggcagtagga cctaatttgt taattaagag tagatgggtga 180
gctgtccctt ttttttgatt aacctaatgg ccttcccagc acgactcgga ttcagctgga 240
gacatcacgg caacttttaa tgaaatgatt tgaagggcca ttaagaggca cttcccgtta 300
ttaaggagtt catctgcact gataacttct tggcagctga gctggtcgga gctgtggccc 360
aaacgcacac ttggcttttg gttttgagat acaactctta atcttttagt catgcttgag 420
gggtgatggc cttttcagct ttaacccaat ttgcactgcc ttggaagtgt agccaggaga 480
atacacicac atactcgtgg gcttagaggc cacagcagat gtcattggtc tactgcctga 540
gtcccgtctg tcccatccca ggaccttcca tcggcgagta cctgggagcc cgtgct 596

```

<210> 427

<211> 107

<212> DNA

<213> Homo sapiens

<220>

<221> misc\_feature

<222> (1)...(107)

<223> n = A,T,C or G

<400> 427

```

gaagaattca agttagggtt attcaaaggc cttacngaga atcctanacc caggncaccag 60
cccgggagca gccttanaga gctcctgttt gactgcccgg ctcagng 107

```

<210> 428

<211> 38

<212> DNA

<213> Homo sapiens

<220>

<221> misc\_feature

<222> (1)...(38)

<223> n = A,T,C or G

<400> 428

```

gaacttcena anaangactt tattcactat ttacatt 38

```

<210> 429

<211> 544

<212> DNA

<213> Homo sapiens

<400> 429

```

ctttgctgga cggaataaaa gtggacgcaa gcatgacctc ctgatgaggg cgctgcattt 60
attgaagagc ggctgcagcc ctgcggttca gattaaaatc cgagaattgt atagacgccg 120
atatccacga actccttgaag gactttctga tttatccaca atcaaatcat cggttttcag 180
tttggtatgt ggctcatcac ctgtagaacc tgacttggcc gtggctggaa tccactcgtt 240
gccttccact tcagttacac ctcactcacc atcctctect gttggttctg tgcgtcttca 300
agatactaag cccacatttg agatgcagca gccatctccc ccaattcctc ctgtccatcc 360
tgatgtgcag ttaaaaaatc tgccctttta tgatgtcctt gatgttctca tcaagcccac 420
tggttttagtt caaagcagta ttcagcgatt tcaagagaag ttttttattt ttgctttgac 480
acctcaacaa gttagagaga tatgcataac cagggtattt ttgccagggt gtaggagaga 540
ttat 544

```

<210> 430

<211> 507  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> misc\_feature  
 <222> (1)...(507)  
 <223> n = A,T,C or G

<400> 430  
 cttatcncaa tggggctccc aaacttggct gtgcagtgga aactccgggg gaattttgaa 60  
 gaacactgac acccatcttc cccccgaca ctctgattta attgggctgc agtgagaaca 120  
 gagcatcaat ttaaaaagct gcccagaatg ttntcctggg cagcgttggt atctttgccn 180  
 ccttcgtgac tttatgcaat gcatcatgct atttcatacc taatgagga gttccaggag 240  
 attcaaccag gatgtttcta cncctgtggg ttatgacaaa gacaactgcc aaagaatntt 300  
 caagaaggag gactgcaagt atatcgtggt ggagaagaag gacccaaaaa agacctgttc 360  
 tgtcagtga tggataatct aatgtgcttc tagtaggcac agggctccca ggccaggcct 420  
 cattctcttc tggcctctaa tagtcaatga ttgtgtagcc atgcctatca gtaaaaagat 480  
 ttttgagcaa aaaaaaaaaa aaaaaaa 507

<210> 431  
 <211> 392  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> misc\_feature  
 <222> (1)...(392)  
 <223> n = A,T,C or G

<400> 431  
 gaaaattcag aatggataaa aacaaatgaa gtacaaaata tttcagattt acatagcgat 60  
 aaacaagaaa gcacttatca ggaggactta caaatggaag tacactctan aaccatcatc 120  
 tatcatggct aaatgtgaga ttagcacagc tgtattattt gtacattgca aacacctaga 180  
 aagagatggg aaacaaaatc ccaggagttt tgtgtgtgga gtcctgggtt ttccaacaga 240  
 catcattcca gcattctgag attagggnga ttggggatca ttctggagtt ggaatgttca 300  
 acaaaagtga tgttgttagg taaaatgtac aacttctgga tctatgcaga cattgaaggt 360  
 gcaatgagtc tggctttttac tctgctgttt ct 392

<210> 432  
 <211> 387  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> misc\_feature  
 <222> (1)...(387)  
 <223> n = A,T,C or G

<400> 432  
 ggtatccnta cataatcaaa tatagctgta gtacatgttt tcattgngt agattaccac 60  
 aaatgcaagg caacatgtgt agatctcttg tcttattctt ttgtctataa tactgtattg 120  
 ngtagtccaa gctctcggn a gtccagccac tngaaacat gtcctcttta gattaacctc 180  
 gtggacnctn ttgttgnatt gtctgaactg tagngcctg tattttgctt ctgtctgnga 240  
 attctgttgc ttctggggca ttctcttng atgcagagga ccaccacaca gatgacagca 300  
 atctgaattg ntccaatcac agctgcgatt aagacatact gaaatcgta aggaccggga 360  
 acaacgtata gaacactgga gtctttt 387

<210> 433  
 <211> 281  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> misc\_feature  
 <222> (1)...(281)  
 <223> n = A,T,C or G

<400> 433  
 tccsactagc anagaanact gcttcagggg gtgtaaaatg aaaggcttcc acgcagttat 60  
 ctgattaaaag aacactaaga gagggacaag gctagaagcc gcaggatgtc tacactatag 120  
 caggencatc ttgggttggc tggaggagct gtggaaaaca tggagagatt ggcgctggag 180  
 atgcgcgtgg ctatctctcn ttgntattac accagngagg ntctctgtnt gcccaactgg 240  
 tnnaaaaccg ntatccata atgatagaat aggacacaca t 281

<210> 434  
 <211> 484  
 <212> DNA  
 <213> Homo sapiens

<400> 434  
 ttttaaaata ancatttagt gctcagtcct tactgagtag tctttctctc cctctctctg 60  
 aatttaattc ttccaacttg caatttgcaa ggattacaca ttccactgtg atgtatattg 120  
 tgttgcaaaa aaaaaaagt gtctttgttt aaaattactt ggtttgtgaa tccatcttgc 180  
 tttttcccca ttggaactag tcattaaccc atctctgaac tggtagaaaa acatctgaag 240  
 agctagtcta tcagcatctg acaggtgaat tggatgggtc tcagaacccat ttcacccaga 300  
 cagcctgttt ctatcctgtt taataaatta gtttgggttc tctacatgca taacaaaccc 360  
 tgetccaatc tgcacataa aagtctgtga cttgaagttt agtcagcacc cccaccaaac 420  
 tttatttttc tatgtgtttt ttgcaacata tgagtgtttt gaaaataaag taccatgtc 480  
 tttta 484

<210> 435  
 <211> 424  
 <212> DNA  
 <213> Homo sapiens

<400> 435  
 ggcgcgtca gaggaggtca ctttctgcct tccacgtcct ccttcaagga agccccatgt 60  
 gggtagcttt caatatcgca ggttcttact cctctgcctc tataagctca aaccaccaa 120  
 cgatcgggca agtaaacccc ctccctcgcc gacttcggaa ctggcgagag ttcagcgcag 180  
 atgggcctgt ggggaggggg caagatagat gagggggagc ggcattggtc ggggtgaccc 240  
 cttggagaga ggaaaaaggc cacaagaggg gctgccaccg ccaactaacg agatggccct 300  
 ggtagagacc ttgggggggc tggaaacctc ggactcccca tgctctaact cccacactct 360  
 gctatcagaa acttaaaactt gaggattttc tctgtttttc actcgcaata aattcagagc 420  
 aaac 424

<210> 436  
 <211> 667  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> misc\_feature  
 <222> (1)...(667)  
 <223> n = A,T,C or G

&lt;400&gt; 436

```
accttgggaa naactctcaca atataaaggg tegttagactt tactccaaat tccaaaaagg 60
tcctggccat gtaatcctga aagttttccc aaggtagcta taaaatcctt ataaggggtgc 120
agcctcttct ggaattcctc tgatttcaaa gtctcactct caagttcttg aaaacgaggg 180
cagttcctga aaggcaggta tagcaactga tcttcagaaa gaggaactgt gtgcaccggg 240
atgggctgcc agagtaggat aggattccag atgctgacac cttctggggg aaacaggggt 300
gccaggtttg tcatagcact catcaaagtc cggccaacgt ctgtgcttcg aatataaacc 360
tgttcattgt tataggactc attcaagaat tttctatata tctttcttat atactctcca 420
agttcataat gctgctccat gccagctgg gtgagttggc caaatccttg tggccatgag 480
gattccttta tggggtcagt gggaaagggt tcaatgggac ttcggtctcc atgccgaaac 540
accaaagtca caaacttcaa ctcttgggt agtacacttc ggtctagcca gaaaaaagc 600
agaaacaaga agccaaggct aaggcttgct gccctgccag gaggaggggt gcagctctca 660
tgttgag 667
```

&lt;210&gt; 437

&lt;211&gt; 693

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 437

```
ctacgtctca accctcattt ttaggtaagg aatcttaagt ccaaagatat taagtgactc 60
acacagccag gtaaggaaag ctggattggc aactaggac tctaccatac cgggttttgt 120
taaagctcag gttaggaggc tgataagctt ggaaggaaact tcagacagct ttttcagatc 180
ataaaaagata attcttagcc catgtttctt tccagagcag acctgaaatg acagcacagc 240
aggtaactct ctatttttcac cctcttgcct tctactctct ggcagtcaga cctgtgggag 300
gccatgggag aaagcagctc tctggatggt tgtacagatc atggactatt ctctgtggac 360
catttctcca ggttaccta ggtgtcacta ttggggggac agccagcatc tttagctttc 420
atgtgagttt ctgtctgtct tcagtagagg aaacttttgc tcttcacact tcacatctga 480
acacctaaact gctgttgctc ctgaggtggg gaaagacaga tatagagctt acagtattta 540
tctatattct aggcactgag ggctgtgggg taccttgtgg tgccaaaaca gatcctgttt 600
taaggacatg ttgcttcaga gatgtctgta actatctggg ggctctgttg gctctttacc 660
ctgcatcatg tgctctcttg gctgaaaatg acc 693
```

&lt;210&gt; 438

&lt;211&gt; 360

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 438

```
ctgcttatca caatgaatgt tctcctgggc agcgttggtga tctttgccac cttcgtgact 60
ttatgcaatg catcatgcta ttccatacct aatgaggagg ttccaggaga ttcaaccagg 120
atgtttctac acctgtgggt tatgacaaag acaactgcc aagaatcttc aagaaggagg 180
actgcaagta tatctgggtg agaagaagga ccaaaaaaag acctgttctg tcagtgaatg 240
gataatctaa tgtgcttcta gtaggcacag ggctcccagg ccaggcctca ttctcctctg 300
gcctctaata gtcaataatt gtgtagccat gcctatcagt aaaaagattt ttgagcaaac 360
```

&lt;210&gt; 439

&lt;211&gt; 431

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; (1)...(431)

&lt;223&gt; n = A,T,C or G

&lt;400&gt; 439

```
gttccctnnta actcctgcc aaaaacagctc tctcaacat gagagctgca cccctcctcc 60
```

```

tggecagggc agcaagcett agcettgggt tcttgtttct gcttttttct tggctagacc 120
gaagtgtact agccaaggag ttgaagtttg tgactttggg gtttcggcat ggagaccgaa 180
gtccatttga cacttttccc actgacccca taaaggaatc ctcatggcca caaggatttg 240
gtcaactcac ccagctgggc atggagcagc attatgaact tggagagtat ataagaaaga 300
gatatagaaa attcttgaat gagtccctata aacatgaaca ggtttatatt cgaagcacag 360
acuttgaccg gactttgatg agtgctatga caaacctggc agcccgtcga cgcggcccg 420
aatttagtag t
431

```

&lt;210&gt; 440

&lt;211&gt; 523

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 440

```

agagataaag cttaggtcaa agttcataga gttcccatga actatatgac tggccacaca 60
ggatcttttg tatttaagga ttctgagatt ttgcttgagc aggattagat aaggctgttc 120
tttaaatgtc tgaaatggaa cagatttcaa aaaaaaaccc cacaatctag ggtgggaaca 180
aggaaggaaa gatgtgaata ggctgatggg caaaaaacca atttaccat cagttccagc 240
cttctctcaa ggagaggcaa agaaaggaga tacagtggag acatctggaa agttttctcc 300
actggaaaac tgctactatc tgtttttata tttctgttaa aatatatgag gctacagaac 360
taaaaattaa aacctctttg tgtcccttg tcttggaaaca tttatgttcc ttttaaagaa 420
acaaaaatca aactttacag aaagatttga tgtatgtaat acatatagca gctcttgaag 480
tatatatatc atagcaaata agtcatctga tgagaacaag cta
523

```

&lt;210&gt; 441

&lt;211&gt; 430

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 441

```

gttcctccta actcctgcc aaaaacagctc tcttcaacat gagagctgca cccctcctcc 60
tggccagggc agcaagcett agcettgggt tcttgtttct gcttttttct tggctagacc 120
gaagtgtact agccaaggag ttgaagtttg tgactttggg gtttcggcat ggagaccgaa 180
gtccatttga cacttttccc actgacccca taaaggaatc ctcatggcca caaggatttg 240
gccaactcac ccagctgggc atggagcagc attatgaact tggagagtat ataagaaaga 300
gatatagaaa attcttgaat gagtccctata aacatgaaca ggtttatatt cgaagcacag 360
acgttgaccg gactttgatg agtgctatga caaacctggc agcccgtcga cgcggcccg 420
aatttagtag
430

```

&lt;210&gt; 442

&lt;211&gt; 362

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 442

```

ctaaggaatt agtagtggtc ccatcacttg tttggagtgt gctattctaa aagattttga 60
tttcttgtaa tgacaattat attttaactt tgggtgggga aagagttata ggaccacagt 120
cttcaacttc gatacttgta aattaacttt ttattgcact tgttttgacc attaatgtat 180
atgttttagaa atggtcattt tacggaaaaa tttagaaaaa tctgataata gtgcagaata 240
aatgaattaa tgttttactt aatttatatt gaactgtcaa tgacaaataa aaattctttt 300
tgattatatt ttgttttcat ttaccagaat aaaaactaag aattaaaagt ttgattacag 360
tc
362

```

&lt;210&gt; 443

&lt;211&gt; 624

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

<220>  
 <221> misc\_feature  
 <222> (1)...(624)  
 <223> n = A,T,C or G

<400> 443  
 tttttttttt gcaacacaaat atacatcaca gtgaaatgtg taatccttgc aaattgcaag 60  
 ttgaaagaat taaattcaga ggaggggaga gaaagagtac tcagtaggga ctgagcacta 120  
 aatgcttatt ttaaaagaaa tgtaaagagc agaaagcaat tcaggctacc ctgccttttg 180  
 tgctggctag tactccggtc ggtgtcagca gcacgtggca ttgaacattg caatgtggag 240  
 cccaaaccac agaaaatggg gtgaaattgg ccaactttct attaacttgg cttectgttt 300  
 tataaaatat tgtgaataat atcacctact tcaaagggca gttatgaggc ttaaataaac 360  
 taacgcctac aaaacactta aacatagata acataggtgc aagtactatg tatctggtac 420  
 atggtaaaca tccttattat taaagtcaac gctaaaatga atgtgtgtgc atatgctaata 480  
 agtacagaga gagggcactt aaaccaacta agggcctgga gggaagggtt cctggaaaga 540  
 ngatgcttgt gctgggtcca aatcttggtc tactatgacc ttggccaaat tatttaaact 600  
 ttgtccctat ctgctaaaca gatc 624

<210> 444  
 <211> 425  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> misc\_feature  
 <222> (1)...(425)  
 <223> n = A,T,C or G

<400> 444  
 gcacatcatt nntcttgcatt tctttgagaa taagaagatc agtaaatagt tcagaagtgg 60  
 gaagctttgt ccaggcctgt gtgtgaaccc aatgttttgc ttagaaatag aacaagtaag 120  
 ttcattgcta tagcataaca caaaatttgc ataagtgttg gtcagcaaat ccttgaatgc 180  
 tqcttaattgt gagaggttgg taaaatcctt tgtgcaaacac tctaactccc tgaatgtttt 240  
 gctgtgctgg gacctgtgca tgccagacaa ggccaagctg gctgaaagag caaccagcca 300  
 cctctgcaat ctgccacetc ctgctggcag gatttgtttt tgcacccctg gaagagccaa 360  
 ggaggcacca gggcataagt gagtagactt atggtcgacg cggccgcgaa tttagtagta 420  
 gtaga 425

<210> 445  
 <211> 414  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> misc\_feature  
 <222> (1)...(414)  
 <223> n = A,T,C or G

<400> 445  
 catgtttatg nttttggatt actttgggca cctagtgttt ctaaatacgtc tatcattctt 60  
 ttctgttttt caaaagcaga gatggccaga gtctcaacaa actgtatctt caagtctttg 120  
 tgaaattctt tgcattgtgc agattatttg atgtagtttc ctttaactag catataaatc 180  
 tgggtgtgtt cagataaatg aacagcaaaa tgtggtggaa ttaccatttg gaacattgtg 240  
 aatgaaaaat tgtgtctcta gattatgtaa caaataacta tttcctaacc attgatcttt 300  
 ggatttttat aatcctactc acaaatgact aggtttctcc tcttgtattt tgaagcagt 360  
 tgggtgctgg attgataaaa aaaaaaaaag tcgacgcggc cgcaattta gtag 414

<210> 446

<211> 631  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> misc\_feature  
 <222> (1)...(631)  
 <223> n = A,T,C or G

<400> 446  
 acaaaattaga anaaagtgcc agagaacacc acataccttg tccggaacat tacaatggct 60  
 tctgcatgca tgggaagtgt gagcattcta tcaatatgca ggagccatct tgcaggtgtg 120  
 atgctggtta tactggacaa cactgtgaaa aaaaggacta cagtgttcta tacgttggtc 180  
 cccgtcctgt acgatttcag tatgtcttaa tccagctgt gattggaaca attcagattg 240  
 ctgtcatctg tgtggtggtc ctctgcatca caagggccaa actttaggta atagcattgg 300  
 actgagattt gtaaaccttc caacctcca ggaaatgcc cagaagcaac agaattcaca 360  
 gacagaagca aaatacaggg cactacagtt cagacaatac aacaagagcg tccacgaggt 420  
 taatctaaag ggagcatgtt tcacagtggc tggactaccg agagcttggg ctacacaata 480  
 cagtattata gacaaaagaa taagacaaga gatctacaca tgttgccctg catttggtgtg 540  
 aatctacacc aatgaaaaca tgtactacag ctatatattga ttatgtatgg atatatttga 600  
 aatagctaac attgtcttga tgtttttct g 631

<210> 447  
 <211> 585  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> misc\_feature  
 <222> (1)...(585)  
 <223> n = A,T,C or G

<400> 447  
 ccttgggaaa antntcacaa tataaagggt cgtagaacttt actccaaatt ccaaaaaggt 60  
 tctggccatg taatcctgaa agttttccca aggtagctat aaaatcctta taagggtgca 120  
 gccctctctg gaattcctct gatttcaaag tctcactctc aagttcttga aaacgagggc 180  
 agttcctgaa aggcaggtat agcaactgat cttcagaaaag aggaactgtg tgcaccggga 240  
 tgggctgcca gagtaggata ggattccaga tgetgacacc ttctggggga aacagggctg 300  
 ccaggtttgt catagcactc atcaaagtcc ggtcaacgtc tgtgcttcga atataaacct 360  
 gttcatgttt ataggactca ttcaagaatt ttctatatct ctttcttata tactctccaa 420  
 gttcataatg ctgctccatg cccagctggg tgagttggcc aaatccttgt ggccatgagg 480  
 attcctttat ggggtcagtg ggaaagggtg caatgggact tccgtctcca tgccgaaaca 540  
 ccaaagtcac aaacttcaac tcttggcta gtacacttcg gtcta 585

<210> 448  
 <211> 93  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> misc\_feature  
 <222> (1)...(93)  
 <223> n = A,T,C or G

<400> 448  
 tgcctgtggg tcattctgan ncccgaactg acntgccag ccttgcgan gggccnccat 60  
 ggctccctag tgccctggag agganggggc tag 93

<210> 449  
 <211> 706  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> misc\_feature  
 <222> (1)...(706)  
 <223> n = A,T,C or G

<400> 449  
 ccaagttcat gctntgtgct ggacgctgga caggggggcaa aagcnnntgc tcgtgggtca 60  
 ttctgancac cgaactgacc atgccagccc tgccgatggt cctccatggc tccctagtgc 120  
 cctggagagg aggtgtctag tcagagagta gtccctggaag gtggcctctg ngaggagcca 180  
 cggggacagc atcctgcaga tggtcgggag cgccccattc gccattcagg ctgcgcaact 240  
 gttgggaagg gcgatcggtg cgggcctctt cgctattacg ccagctggcg aaagggggat 300  
 gtgctgcaag gcgattaagt tgggtaacgc cagggttttc ccagtcncga cgttgtaaaa 360  
 cgacggccag tgaattgaat ttaggtgacn ctatagaaga gctatgacgt cgcattgcacg 420  
 cgtacgtaag cttggatcct ctagagcggc cgcctactac tactaaattc gcggccgcgt 480  
 cgacgtggga tccnactga gagagtggag agtgacatgt gctggacnct gtccatgaag 540  
 cactgagcag aagctggagg cacaacgcnc cagacactca cagctactca ggaggctgag 600  
 aacaggttga acctgggagg tggaggttgc aatgagctga gatcaggccn ctgcncacca 660  
 gcatggatga cagagtgaaa ctccatctta aaaaaaaaaa aaaaaa 706

<210> 450  
 <211> 493  
 <212> DNA  
 <213> Homo sapiens

<400> 450  
 gagacggagt gtcactctgt tgcccaggct ggagtgcagc aagacactgt ctaagaaaaa 60  
 acagttttta aaggtaaaaac aacataaaaa gaaatatcct atagtggaaa taagagagtc 120  
 aaatgaggct gagaacttta caaagggatc ttacagacat gtcgccaata tcaactgcatq 180  
 agcctaagta taagaacaac ctttggggag aaaccatcat ttgacagtga ggtacaattc 240  
 caagtcaagt agtgaaatgg gtggaattaa actcaaatta atcctgccag ctgaaacgca 300  
 agagacactg tcagagagtt aaaaagttag ttctatccat gaggtgattc cacagtcttc 360  
 tcaagtcaac acatctgtga actcacagac caagttctta aaccactgtt caaactctgc 420  
 tacacatcag aatcacctgg agagctttac aaactcccat tgccgagggt cgacgcggcc 480  
 gcgaatttag tag 493

<210> 451  
 <211> 501  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> misc\_feature  
 <222> (1)...(501)  
 <223> n = A,T,C or G

<400> 451  
 gggcgcgctc cattcgccat tcaggctgag caactgttgg gaaggcgcat cggtgcgggc 60  
 ctcttcgcta ttacgccagc tggcgaaagg gggatgtgct gcaaggcgat taagttgggt 120  
 aacgccaggg ttttccagct cncgacgttg taaaacgacg gccagtgaat tgaatttagg 180  
 tgacnctata gaagagctat gacgtcgcat gcacgcgtac gtaagcttgg atcctctaga 240  
 gcggccgcct actactacta aattcgcggc cgcgtcgacg tgggatccnc actgagagag 300  
 tggagagtga catgtgctgg acnctgtcca tgaagcactg agcagaagct ggaggcacia 360  
 cgcncagagc actcacagct actcaggagg ctgagaacag gttgaacctg ggaggtggag 420



gttgcaatga gctgagatca ggcnctgcn cccagcatg gatgacagag tgaaactcca 480  
tcttaaaaaa aaaaaaaaaa a 501

<210> 452  
<211> 51  
<212> DNA  
<213> Homo sapiens

<220>  
<221> misc\_feature  
<222> (1)...(51)  
<223> n = A,T,C or G

<400> 452  
agaagggttc accnttataa cnccttttag gatgggnntt ggggagcaag c 51

<210> 453  
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<212> DNA  
<213> Homo sapiens

<220>  
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<223> n = A,T,C or G

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ttcacccana cagcctgttt ctatcctgtt taataaatta gtttgggttc tctacatgca 180  
taacaaaccc tgcctcaatc tgtcacataa aagtctgtga cttgaagttt antcagcacc 240  
cccacaaac tttatttttc tatgtgtttt ttgcaacata tgagtgtttt gaaaataagg 300  
taccatgtc tttatta 317

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<212> DNA  
<213> Homo sapiens

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agaagaccaa attcttctgc atcccagctt gcaaacaaaa ttgttcttct aggtctccac 180  
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<212> DNA  
<213> Homo sapiens

<400> 455  
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gtttcaacgc attgatgact tctccaagga tcttcctttg gcatcgacca cattcagggg 180  
caaagaattt ctcatagcac agtcacaaat acagggtctc tttctcctct a 231

<210> 456  
<211> 231

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 456

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tgcaactcaaa ttccctttatc aggaataact acatagccac tatttacaaa gccattggaa 180
cctttttatt tgggtgcagct gctagtcagt cctgactga cattgccaaag t          231

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&lt;210&gt; 457

&lt;211&gt; 231

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; (1)...(231)

&lt;223&gt; n = A,T,C or G

&lt;400&gt; 457

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tatttgattt tattagcaat ctctttcaga agacccttga gatcattaag ctttgtatcc 180
agttgtctaa atcgatgctt catttcctct gaggtgtcgc tggcttttgt g          231

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&lt;210&gt; 458

&lt;211&gt; 231

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 458

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aggtctgggt cccccactt ccactcccct ctactctctc taggactggg ctggggccaag 60
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acaccctaac cttgggtaac agcatttgga attatcattt gggatgagta gaatttccaa 180
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&lt;210&gt; 459

&lt;211&gt; 231

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 459

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ggtaccgagg ctgctgaca cagagaaacc ccaacgcgag gaaaggaatg gccagccaca 60
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gccctgcact gttttccctc caccacagcc atcctgtccc tcattggctc tgtgttttcc 180
actatacaca gtcaccgtcc caatgagaaa caagaaggag caccctccac a          231

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&lt;210&gt; 460

&lt;211&gt; 231

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 460

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cccacctccc cacacgcaca cgccagcct ggagcccaca gaagggtcct cctgcagcca 180
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 <212> DNA  
 <213> Homo sapiens

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 gtgggggttca gtgaggagtg ggaaattggt tcagcagaac caagccgttg ggtgaataag 180  
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 <212> DNA  
 <213> Homo sapiens

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 <213> Homo sapiens

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 catttgacag gtgtcttttc ctctggacct cgggtgtcccc atctgagtga gaaaaggcag 180  
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 <212> DNA  
 <213> Homo sapiens

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 cctgcttcag tgactgtgtg cctgtagtcc cagctactcg ggagtctgtg tgaggccagg 180  
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<210> 465  
 <211> 231  
 <212> DNA  
 <213> Homo sapiens

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 aggatggcac aatttttget tgtgttcata atatactcag attagttcag ctccatcaga 180  
 taaactggag acatgcagga cattagggta gtgtttagc tctggtaaat a 231

<210> 466  
 <211> 231  
 <212> DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 466

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cctgtgcaat caaatattgt ggagaattcc ctagctggag aagtcacaaa gactataggc 180
aataatggag accagtccca caagatgaca accagtcggt gtgtgcggct g          231

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&lt;210&gt; 467

&lt;211&gt; 311

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 467

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ctgcagcaga c          311

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&lt;210&gt; 468

&lt;211&gt; 3112

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 468

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&lt;210&gt; 469

&lt;211&gt; 2229

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 469

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2229

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&lt;210&gt; 470

&lt;211&gt; 2426

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 470

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2426

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&lt;210&gt; 471

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 <212> DNA  
 <213> Homo sapiens

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&lt;210&gt; 474

&lt;211&gt; 1594

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 474

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 ttggaatcct gcagatataa taatgataat taaacaaaaa actcagagaa actgccaacc 2520  
 ctaggatgaa gtatattgtt actgtgcttt gggattaaaa taagtaacta cagtttatag 2580  
 aacttttata ctgatacaca gacactaaaa agggaaaggg tttagatgag aagctctgct 2640  
 atgcaatcaa gaatctcagc cactcatctt tgtaggggct gcaggagctc cctgtaaaga 2700  
 gaggttatgg agtctgtagc ttcaggtaag atacttaaaa ccttccagag tttctccatt 2760  
 ctctccata gtttccccaa aaaggttatg acactttata agaatgcttc acttgtgaaa 2820  
 aacaaatata aaagtcttct tgtagattat ttttaaggac aaatctttat tccatgttta 2880  
 atttatttag ctttccctgt agctaataat tcatgctgaa cacattttta atgctgtaaa 2940  
 ggtagataat gtaatttatg tatcattaat gcctctttag tagtttagag aaaacgtcaa 3000  
 aagaatggc ccagaataa gcttcttgat ttgtaaaatt ctatgtcatt ggctcaaatt 3060

```
<210> 477
<211> 140
<212> PRT
<213> Homo sapiens
```

```

<400> 477
Met Asp Gly His Thr Asp Ile Trp Arg Asn His Met Asp Thr Pro Pro
                    5                      10                      15

His Tyr His Arg Asp Thr Asp Thr Arg Arg His His His Met Asp Thr
                    20                      25                      30

Leu Ser His Tyr His Arg Asp Thr Arg His His Thr Val Thr Trp Thr
                    35                      40                      45

His His His Thr His Glu His Thr Asp Thr Leu Pro Tyr Gly His Trp
                    50                      55                      60

His Thr His Cys His Thr Val Thr Trp Thr His Leu His Thr Ile Thr
65                      70                      75                      80

Pro Pro His Thr Leu Pro Val Asp Thr Arg Thr His Arg His Cys His
                    85                      90                      95

Thr Asp Thr Gln Asn Thr Val Thr Arg Arg His His His Ala Asp Thr
                    100                      105                      110

Pro Pro Leu Trp Cys Arg Leu Asn Tyr Pro Ala Gly Gly Thr Ala Val
                    115                      120                      125

Ala Tyr Ser Cys Leu Ser Asp Trp Leu Ser Pro Gln
130                      135                      140

```

```
<210> 478
<211> 143
<212> PRT
<213> Homo sapiens
```

```

<400> 478
Met Tyr Arg His Thr Glu Thr Leu Pro His Gly Asp Thr Val Thr Gln
                    5                      10                      15

Ser His Gly His Thr Gly Ile Val Thr Trp Thr Asp Thr Gln Thr Tyr
                20                      25                      30

Gly Glu Ile Thr Trp Thr His His His Thr Ile Thr Gly Thr Gln Thr
                35                      40                      45

His Gly Asp Ile Thr Thr Trp Thr His Cys His Thr Thr Thr Gly Thr

```

50	55	60
Arg Asp Ile Thr Leu Ser His Gly His Thr Ile Thr His Met Asn Thr		
65	70	75 80
Pro Thr His Cys His Met Asp Thr Gly Thr His Thr Ala Thr Leu Ser		
	85	90 95
His Gly His Thr Ser Thr Pro Ser His His His Thr His Cys Leu Trp		
	100	105 110
Thr Gln Gly His Thr Asp Thr Val Thr Gln Ile His Lys Thr Leu Ser		
	115	120 125
His Gly Asp Ile Thr Met Gln Ile His His His Ser Gly Ala Val		
130	135	140

&lt;210&gt; 479

&lt;211&gt; 222

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 479

Met Tyr Arg His Thr Glu Thr Leu Pro His Gly Asp Thr Val Thr Gln		
	5	10 15
Ser His Glu His Thr Gly Ile Val Thr Trp Thr Asp Thr Gln Thr Tyr		
	20	25 30
Gly Glu Ile Thr Leu Thr His His His Thr Ile Thr Gly Thr Gln Thr		
	35	40 45
His Gly Asp Ile Thr Thr Trp Thr His Cys His Thr Thr Thr Gly Thr		
	50	55 60
Arg Asp Ile Thr Leu Ser His Gly His Thr Ile Thr His Met Asn Thr		
65	70	75 80
Pro Thr His Cys His Met Asp Thr Ala Thr His Thr Ala Thr Leu Ser		
	85	90 95
His Gly His Thr Ser Ile Pro Ser His His His Thr His Cys His Val		
	100	105 110
Asp Thr Arg Thr His Arg His Cys His Thr Asp Thr Gln Asn Thr Val		
	115	120 125
Thr Arg Arg His His His Ala Asp Thr Pro Pro His Gly His Ser Thr		
	130	135 140
Arg His Ser Ala Thr Gln Ile His His His Thr Glu Met Arg Thr His		
145	150	155 160
Cys His Thr Asp Thr Thr Thr Ser Leu Pro His Phe His Val Ser Ala		
	165	170 175
Gly Gly Val Gly Pro Thr Thr Leu Gly Ser Asn Arg Glu Ile Thr Trp		

180                      185                      190  
 Thr Tyr Ser Glu Gly Lys Ile Phe Phe Tyr Phe Leu Gly Asn Gln Ala  
           195                      200                      205  
 Arg Leu Cys Leu Lys Lys Arg Lys Lys Lys Gln Tyr Thr Val  
           210                      215                      220  
  
 <210> 480  
 <211> 144  
 <212> PRT  
 <213> Homo sapiens  
  
 <400> 480  
 Met Glu Pro Tyr Arg Gly Asn Glu Gln Pro Ser Gln Glu Gln Gly Val  
                                  5                      10                      15  
 Cys Cys Leu Trp Gly Leu Gln Ser Leu Pro Gln Gly Ser Tyr Val Thr  
                                  20                      25                      30  
 Val Gly Phe Leu Val Val Lys Arg Gln Thr Ile Gly Arg Leu Glu Arg  
                                  35                      40                      45  
 Asp Phe Met Phe Lys Cys Arg Lys Gln Pro Gly Leu Pro Pro Ser Gly  
                                  50                      55                      60  
 Leu Cys Leu Leu Trp Pro Trp Pro Asn Leu Glu Phe Gly Arg Arg Gln  
                                  65                      70                      75                      80  
 Asp Arg Leu Thr Trp Ser Ser Val Ser Val Ala Gly Val Cys Ala Cys  
                                  85                      90                      95  
 Arg Ala Arg Pro Gly Trp Leu Gly Glu Gln Pro Ala Thr Ser Ala Gly  
                                  100                      105                      110  
 Val Arg Leu Glu Gln Val Glu Gln Pro Pro Ala His Pro Leu Gln Glu  
                                  115                      120                      125  
 Ala Gly Val Ala Arg Phe Pro Arg Pro Glu Trp Val Pro Pro Asn Gly  
                                  130                      135                      140

<210> 481  
 <211> 167  
 <212> PRT  
 <213> Homo sapiens

<400> 481  
 Met His Gly Pro Gln Val Leu Ala Arg Cys Ser Glu Cys Ala Cys Pro  
                                  5                      10                      15  
 Ala Leu Ala Ala Thr Ser Ala Gly Val Arg Leu Glu Gly Val Asp Arg  
                                  20                      25                      30

Pro Pro Thr Leu Pro Ser Gln Gly Ser Gly Trp Pro Cys Ser His Ser  
           35                  40                  45  
 Leu Ser Gly Cys His Leu Met Ala Asp Gly Ala Lys Ala Leu Gly Lys  
           50                  55                  60  
 Ala Asp Gly Pro Trp Pro Tyr Leu Phe Val Arg Arg Thr Asp Val Pro  
           65                  70                  75                  80  
 Cys Pro Ala Ala Ser Glu Val Gly Gly Cys Ala Pro Ser Ser Trp Arg  
                   85                  90                  95  
 Ala Leu Ala Glu Val Thr Gly Cys Ser Leu Gly Pro Leu Gly Leu Ala  
                   100                  105                  110  
 Gln His Ala Gln Ala Ser Val Leu Leu Leu Cys Tyr Lys Trp Ser His  
           115                  120                  125  
 Ile Gly Glu Thr Ser Ser His Leu Arg Ser Lys Val Tyr Ala Ala Phe  
           130                  135                  140  
 Gly Gly Ser Ser Pro Cys Leu Lys Gly Leu Met Ser Leu Trp Ala Ser  
           145                  150                  155                  160  
 Trp Leu Ser Arg Gly Arg Pro  
                   165

&lt;210&gt; 482

&lt;211&gt; 143

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 482

Met Glu Pro Tyr Arg Gly Asn Lys Lys Gln Val Gln Glu Lys Gly Val  
                   5                  10                  15  
 Pro Cys Leu Trp Gly Ser Ser Pro Cys Leu Arg Cys His Met Ala Leu  
           20                  25                  30  
 Arg Ala Ser Trp Leu Pro Gly Gly Gly Pro Gln Ala Ile Leu Gly Arg  
           35                  40                  45  
 Thr Leu Cys Ser Ser Ala Glu Ser Ser Gln Asp Cys His Pro Gly Gly  
           50                  55                  60  
 Pro Ser Ile Ala Leu Ala Lys Pro Cys Arg Gly Val Trp Leu Leu Phe  
           65                  70                  75                  80  
 Glu Pro Ala Trp Pro Pro Trp His Ala Arg Ala Pro Gly Ala Gly Thr  
                   85                  90                  95  
 Leu Leu Arg Val Cys Leu Ser Cys Leu Gly Cys His Leu Cys Gly Gly  
           100                  105                  110  
 Ala Ser Gly Gly Gly Gly Pro Ala Thr Asn Leu Thr Gln Ser Arg Lys  
           115                  120                  125

169

Trp Met Ala Met Phe Pro Gln Pro Glu Trp Leu Pro Pro Asp Gly  
 130 135 140

&lt;210&gt; 483

&lt;211&gt; 143

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 483

Met Glu Thr Gln Arg Gly Asn Lys Gln Arg Ala Gln Glu Gln Gly Val  
 5 10 15

Cys Cys Leu Trp Gly Ser Ser Pro Cys Leu Gly Ser Tyr Gly Thr Ala  
 20 25 30

Gly Phe Leu Val Ala Lys Arg Arg Thr Thr Gly Leu Leu Glu Glu Asp  
 35 40 45

Phe Thr Phe Lys Cys Arg Lys Gln Pro Lys Leu Pro Ser Met Arg Leu  
 50 55 60

Ser Leu Leu Trp Pro Trp Arg Asp Leu Lys Phe Val Pro Arg Gln Asp  
 65 70 75 80

Lys Leu Thr Arg Ser Ser Val Ser Val Ala Gly Ala Tyr Ala Cys Arg  
 85 90 95

Ala Gly Pro Gly Trp Leu Lys Glu Gln Pro Ala Thr Ser Ala Arg Val  
 100 105 110

Arg Leu Val Gln Ala Glu His Pro Pro Pro His Pro Leu Glu Glu Val  
 115 120 125

Gly Met Ala Arg Phe Pro Gln Pro Glu Cys Leu Pro Pro Tyr Cys  
 130 135 140

&lt;210&gt; 484

&lt;211&gt; 30

&lt;212&gt; PRT

&lt;213&gt; Homo Sapien

&lt;400&gt; 484

Thr Ala Ala Ser Asp Asn Phe Gln Leu Ser Gln Gly Gly Gln Gly Phe  
 1 5 10 15

Ala Ile Pro Ile Gly Gln Ala Met Ala Ile Ala Gly Gln Ile  
 20 25 30

&lt;210&gt; 485

&lt;211&gt; 31

&lt;212&gt; DNA

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; Made in a lab

&lt;400&gt; 485

gggaagctta tcacctatgt gccgcctctg c

31



<210> 486  
 <211> 27  
 <212> DNA  
 <213> Artificial Sequence

<220>  
 <223> Made in a lab

<400> 486  
 gcgaattctc acgctgagta ttggcc 27

<210> 487  
 <211> 36  
 <212> DNA  
 <213> Artificial Sequence

<220>  
 <223> Made in a lab

<400> 487  
 ccgaattct tagctgccca tccgaacgcc ttcato 36

<210> 488  
 <211> 33  
 <212> DNA  
 <213> Artificial Sequence

<220>  
 <223> Made in a lab

<400> 488  
 gggaagcttc ttccccggt gcaccagctg tgc 33

<210> 489  
 <211> 19  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Made in a lab

<400> 489  
 Met Asp Arg Leu Val Gln Arg Phe Gly Thr Arg Ala Val Tyr Leu Ala  
 1 5 10 15  
 Ser Val Ala

<210> 490  
 <211> 20  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Made in a lab

<400> 490  
 Tyr Leu Ala Ser Val Ala Ala Phe Pro Val Ala Ala Gly Ala Thr Cys



20

<210> 495  
 <211> 20  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Made in a lab

<400> 495  
 Asp Ser Leu Met Thr Ser Phe Leu Pro Gly Pro Lys Pro Gly Ala Pro  
 1 5 10 15  
 Phe Pro Asn Gly  
 20

<210> 496  
 <211> 21  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Made in a lab

<400> 496  
 Ala Pro Phe Pro Asn Gly His Val Gly Ala Gly Gly Ser Gly Leu Leu  
 1 5 10 15  
 Pro Pro Pro Pro Ala  
 20

<210> 497  
 <211> 20  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Made in a lab

<400> 497  
 Leu Leu Pro Pro Pro Pro Ala Leu Cys Gly Ala Ser Ala Cys Asp Val  
 1 5 10 15  
 Ser Val Arg Val  
 20

<210> 498  
 <211> 20  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Made in a lab

<400> 498  
 Asp Val Ser Val Arg Val Val Val Gly Glu Pro Thr Glu Ala Arg Val  
 1 5 10 15  
 Val Pro Gly Arg  
 20

<210> 499  
 <211> 20  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Made in a lab

<400> 499  
 Arg Val Val Pro Gly Arg Gly Ile Cys Leu Asp Leu Ala Ile Leu Asp  
 1 5 10 15  
 Ser Ala Phe Leu  
 20

<210> 500  
 <211> 20  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Made in a lab

<400> 500  
 Leu Asp Ser Ala Phe Leu Leu Ser Gln Val Ala Pro Ser Leu Phe Met  
 1 5 10 15  
 Gly Ser Ile Val  
 20

<210> 501  
 <211> 20  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Made in a lab

<400> 501  
 Phe Met Gly Ser Ile Val Gln Leu Ser Gln Ser Val Thr Ala Tyr Met  
 1 5 10 15  
 Val Ser Ala Ala  
 20

<210> 502  
 <211> 414  
 <212> DNA  
 <213> Homo Sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(414)  
 <223> n=A,T,C or G

<400> 502  
 caccatggag acaggcctgc gctggctttt cctggctcgt gtgctcaaag gtgtccaatg 60  
 tcagtgggtg gaggagtcog ggggtcgcct ggtcacgcct gggacacctt tgacantcac 120  
 ctgtagagtt tttggaatng acctcagtag caatgcaatg agctgggtcc gccaggctcc 180  
 agggaagggg ctggaatgga tcggagccat tgataattgt ccacantacg cgacctgggc 240

```

gagaggacga ttnatnattt ccaaaacctn gaccacggtg gatttgaaaa tgaccagtc 300
gacacacgag gacacggcca cctatttttg tggcagaatg aatactggta atagtgggtg 360
gagacatatt tggggcccag gcaccctggt caccgtntcc tcagggcaac ctaa 414

```

<210> 503  
 <211> 379  
 <212> DNA  
 <213> Homo Sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(379)  
 <223> n=A,T,C or G

```

<400> 503
atnccatggt gcttgcacaa aggtgtccag tgccagtcgg tggaggagtc cgggggtcgc 60
ctggtcacgc ctgggacacc cctgacactc acctgcaccg tntctggatt ngacatcagt 120
agclatggag tgaactgggt ccgccaggct ccaggggaagg ggctgggata catcggtatca 180
ttagtagtag tgtacattt tacgcgagct gggcgaaagg ccgattcacc atttccaaaa 240
cctngaccac ggtgatttg aaaatcacca gtttgacaac cgaggacacg gccacctatt 300
tntgtgccag aggggggttt aattataaag acatttgggg ccagggcacc ctggtcaccg 360
tntccttaag gcaacctaa 379

```

<210> 504  
 <211> 19  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Made in a lab

```

<400> 504
Gly Phe Thr Asn Tyr Thr Asp Phe Glu Asp Ser Pro Tyr Phe Lys Glu
  1             5             10             15
Asn Ser Ala

```

<210> 505  
 <211> 20  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Made in a lab

```

<400> 505
Lys Glu Asn Ser Ala Phe Pro Pro Phe Cys Cys Asn Asp Asn Val Thr
  1             5             10             15
Asn Thr Ala Asn
                20

```

<210> 506  
 <211> 407  
 <212> DNA  
 <213> Homo Sapien

<400> 506

```

atggagacag gcctgcgctg gcttctcctg gtcgctgctg tcaaaggtgt ccagtgtcag      60
tcgctggagg agtcggggg tcgctgggc acgcctggga caccctgac actcacctgc      120
accgtctctg gattctccct cagtagcaat gcaatgatct gggtcggcca ggctccaggg      180
aaggggctgg aatacatcgg atacattagt tatggtggta gcgcatacta cgcgagctgg      240
gtgaaaggcc gattcaccat ctccaaaacc tcgaccacgg tggatctgag aatgaccagt      300
ctgacaaccg aggacacggc cacctatttc tgtgccagaa atagtgattt tagtggtatg      360
ttgtggggcc caggcacccct ggtcaccgtc tctcagggc aacctaa      407

```

<210> 507  
 <211> 422  
 <212> DNA  
 <213> Homo Sapien

```

<400> 507
atggagacag gcctgcgctg gcttctcctg gtcgctgtgc tcaaaggtgt ccagtgtcag      60
tcggtggagg agtcggggg tcgctgggc acgcctggga caccctgac actcacctgt      120
acagtctctg gattctccct cagcaactac gacctgaact gggtcggcca ggctccaggg      180
aaggggctgg aatggatcgg gatcattaat tatgttggta ggaaggacta cgcgaactgg      240
gcaaaaggcc ggttcaccat ctccaaaacc tcgaccacgg tggatctcaa gatcgccagt      300
ccgacaaccg aggacacggc cacctatttc tgtgccagag ggtggaagtg cgatgagtct      360
ggtcgctgct tgcgcatctg gggcccaggc accctggtca ccgtctcctt agggcaacct      420
aa

```

<210> 508  
 <211> 411  
 <212> DNA  
 <213> Homo Sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(411)  
 <223> n=A,T,C or G

```

<400> 508
atggagacag gcctgcgctg cttctcctgg tcgctgtgct caaaggtgtc cagtgtcagt      60
cgggtggagg gtccgggggt cgcctgggtc cgcctgggac acccctgaca ctcacctgca      120
cagtctctgg aatcgacctc agtagctact gcatgagctg ggtccggccag gctccagggg      180
aggggctgga atggatcgga atcattggta ctctggtga cacatactac gcgagggtgg      240
cgaaaggccg attcaccatc tccaaaacct cgaccacggt gcatntgaaa atcnccagtc      300
cgacaaccga ggacacggcc acctatttct gtgccagaga tcttcgggat ggtagtagta      360
ctggttatta taaaatctgg ggcccaggca ccctgggtcac cgtctccttg g      411

```

<210> 509  
 <211> 15  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Made in a lab

```

<400> 509
Leu Cys Lys Phe Thr Glu Trp Ile Glu Lys Thr Val Gln Ala Ser
 1              5              10              15

```

<210> 510  
 <211> 15  
 <212> PRT  
 <213> Artificial Sequence

```

<220>
<223> Made in a lab

<400> 510
Pro Glu Tyr Asn Arg Pro Leu Leu Ala Asn Asp Leu Met Leu Ile
1          5          10          15

<210> 511
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<223> Made in a lab

<400> 511
Tyr His Pro Ser Met Phe Cys Ala Gly Gly Gly Gln Asp Gln Lys
1          5          10          15

<210> 512
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<223> Made in a lab

<400> 512
Asp Ser Gly Gly Pro Leu Ile Cys Asn Gly Tyr Leu Gln Gly Leu
1          5          10          15

<210> 513
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<223> Made in a lab

<400> 513
Ala Pro Cys Gly Gln Val Gly Val Pro Asx Val Tyr Thr Asn Leu
1          5          10          15

<210> 514
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<223> Made in a lab

<400> 514
Leu Cys Lys Phe Thr Glu Trp Ile Glu Lys Thr Val Gln Ala Ser
1          5          10          15

<210> 515

```

<211> 15  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Made in a lab

<400> 515  
 Met Val Glu Ala Ser Leu Ser Val Arg His Pro Glu Tyr Asn Arg  
 1 5 10 15

<210> 516  
 <211> 15  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Made in a lab

<400> 516  
 Val Ser Glu Ser Asp Thr Ile Arg Ser Ile Ser Ile Ala Ser Gln  
 1 5 10 15

<210> 517  
 <211> 15  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Made in a lab

<400> 517  
 Glu Val Cys Ser Lys Leu Tyr Asp Pro Leu Tyr His Pro Ser Met  
 1 5 10 15

<210> 518  
 <211> 15  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Made in a lab

<400> 518  
 Arg Ala Glu Pro Gly Thr Glu Ala Arg Arg His Tyr Asp Glu Gly  
 1 5 10 15

<210> 519  
 <211> 17  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Made in a lab

<400> 519  
 Arg Ala Glu Pro Gly Thr Glu Ala Arg Arg Asn Tyr Asp Glu Gly Cys  
 1 5 10 15



Gly

<210> 520  
 <211> 25  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Made in a lab

<400> 520  
 Val Gly Glu Gly Leu Tyr Gln Gly Val Pro Arg Ala Glu Pro Gly Thr  
 1 5 10 15  
 Glu Ala Arg Arg His Tyr Asp Glu Gly  
 20 25

<210> 521  
 <211> 21  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Made in a lab

<400> 521  
 Ala Pro Phe Pro Asn Gly His Val Gly Ala Gly Gly Ser Gly Leu Leu  
 1 5 10 15  
 Pro Pro Pro Pro Ala  
 20

<210> 522  
 <211> 20  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Made in a lab

<400> 522  
 Leu Leu Val Val Pro Ala Ile Lys Lys Asp Tyr Gly Ser Gln Glu Asp  
 1 5 10 15  
 Phe Thr Gln Val  
 20

<210> 523  
 <211> 254  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Made in a lab

<220>  
 <221> VARIANT  
 <222> (1)...(254)  
 <223> Xaa = any amino acid

&lt;400&gt; 523

```

Met Ala Thr Ala Gly Asn Pro Trp Gly Trp Phe Leu Gly Tyr Leu Ile
 1          5          10          15
Leu Gly Val Ala Gly Ser Leu Val Ser Gly Ser Cys Ser Gln Ile Ile
          20          25          30
Asn Gly Glu Asp Cys Ser Pro His Ser Gln Pro Trp Gln Ala Ala Leu
          35          40          45
Val Met Glu Asn Glu Leu Phe Cys Ser Gly Val Leu Val His Pro Gln
          50          55          60
Trp Val Leu Ser Ala Thr His Cys Phe Gln Asn Ser Tyr Thr Ile Gly
          65          70          75          80
Leu Gly Leu His Ser Leu Glu Ala Asp Gln Glu Pro Gly Ser Gln Met
          85          90          95
Val Glu Ala Ser Leu Ser Val Arg His Pro Glu Tyr Asn Arg Pro Leu
          100          105          110
Leu Ala Asn Asp Leu Met Leu Ile Lys Leu Asp Glu Ser Val Ser Glu
          115          120          125
Ser Asp Thr Ile Arg Ser Ile Ser Ile Ala Ser Gln Cys Pro Thr Ala
          130          135          140
Gly Asn Ser Cys Leu Val Ser Gly Trp Gly Leu Leu Ala Asn Gly Arg
          145          150          155          160
Met Pro Thr Val Leu Gln Cys Val Asn Val Ser Val Val Ser Glu Glu
          165          170          175
Val Cys Ser Lys Leu Tyr Asp Pro Leu Tyr His Pro Ser Met Phe Cys
          180          185          190
Ala Gly Gly Gly Gln Xaa Gln Xaa Asp Ser Cys Asn Gly Asp Ser Gly
          195          200          205
Gly Pro Leu Ile Cys Asn Gly Tyr Leu Gln Gly Leu Val Ser Phe Gly
          210          215          220
Lys Ala Pro Cys Gly Gln Val Gly Val Pro Gly Val Tyr Thr Asn Leu
          225          230          235          240
Cys Lys Phe Thr Glu Trp Ile Glu Lys Thr Val Gln Ala Ser
          245          250

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&lt;210&gt; 524

&lt;211&gt; 765

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 524

```

atggccacag caggaaatcc ctggggctgg ttcttgggggt acctcatcct tgggtgtcgca      60
ggatcgctcg tctctggtag ctgcagccaa atcataaacg gcgaggactg cagcccgcac      120
tcgcagccct ggcaggcggc actggtcatt gaaaacgaat tggtctgctc gggcgctcctg      180
gtgcatccgc agtgggtgct gtcagccgca cactgtttcc agaactccta caccatcggg      240
ctgggcctgc acagtcttga ggccgaccaa gagccaggga gccagatggt ggaggccagc      300
ctctccgtac ggcaccaga gtacaacaga cccttgctcg ctaacgacct catgetcatc      360
aagttggacg aatccgtgtc cgagtctgac accatccgga gcatcagcat tgcttcgcag      420
tgccctaccg cggggaatc ttgcctcgtt tctggtggg gtctgctggc gaacggcaga      480
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&lt;210&gt; 525

&lt;211&gt; 254

&lt;212&gt; PRT

&lt;213&gt; Homo sapien

&lt;400&gt; 525

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Met Ala Thr Ala Gly Asn Pro Trp Gly Trp Phe Leu Gly Tyr Leu Ile
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Leu Gly Val Ala Gly Ser Leu Val Ser Gly Ser Cys Ser Gln Ile Ile
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Asn Gly Glu Asp Cys Ser Pro His Ser Gln Pro Trp Gln Ala Ala Leu
 35          40          45
Val Met Glu Asn Glu Leu Phe Cys Ser Gly Val Leu Val His Pro Gln
 50          55          60
Asp Val Leu Ser Ala Ala His Cys Phe Gln Asn Ser Tyr Thr Ile Gly
 65          70          75          80
Leu Gly Leu His Ser Leu Glu Ala Asp Gln Glu Pro Gly Ser Gln Met
 85          90          95
Val Glu Ala Ser Leu Ser Val Arg His Pro Glu Tyr Asn Arg Pro Leu
100          105          110
Leu Ala Asn Asp Leu Met Leu Ile Lys Leu Asp Glu Ser Val Ser Glu
115          120          125
Ser Asp Thr Ile Arg Ser Ile Ser Ile Ala Ser Gln Cys Pro Thr Ala
130          135          140
Gly Asn Ser Cys Leu Val Ser Gly Trp Gly Leu Leu Ala Asn Gly Arg
145          150          155          160
Met Pro Thr Val Leu Gln Cys Val Asn Val Ser Val Val Ser Glu Glu
165          170          175
Val Cys Ser Lys Leu Tyr Asp Pro Leu Tyr His Pro Ser Met Phe Cys
180          185          190
Ala Gly Gly Gly Gln Asp Gln Lys Asp Ser Cys Asn Gly Asp Ser Gly
195          200          205
Gly Pro Leu Ile Cys Asn Gly Tyr Leu Gln Gly Leu Val Ser Phe Gly
210          215          220
Lys Ala Pro Cys Gly Gln Val Gly Val Pro Gly Val Tyr Thr Asn Leu
225          230          235          240
Cys Lys Phe Thr Glu Trp Ile Glu Lys Thr Val Gln Ala Ser
245          250

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&lt;210&gt; 526

&lt;211&gt; 963

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 526

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&lt;210&gt; 527

&lt;211&gt; 320

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 527

Met Ser Ser Cys Asn Phe Thr His Ala Thr Phe Val Leu Ile Gly Ile  
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Pro Gly Leu Glu Lys Ala His Phe Trp Val Gly Phe Pro Leu Leu Ser  
                   20                  25                  30

Met Tyr Val Val Ala Met Phe Gly Asn Cys Ile Val Val Phe Ile Val  
                   35                  40                  45

Arg Thr Glu Arg Ser Leu His Ala Pro Met Tyr Leu Phe Leu Cys Met  
                   50                  55                  60

Leu Ala Ala Ile Asp Leu Ala Leu Ser Thr Ser Thr Met Pro Lys Ile  
                   65                  70                  75                  80

Leu Ala Leu Phe Trp Phe Asp Ser Arg Glu Ile Ser Phe Glu Ala Cys  
                   85                  90                  95

Leu Thr Gln Met Phe Phe Ile His Ala Leu Ser Ala Ile Glu Ser Thr  
                   100                  105                  110

Ile Leu Leu Ala Met Ala Phe Asp Arg Tyr Val Ala Ile Cys His Pro  
                   115                  120                  125

Leu Arg His Ala Ala Val Leu Asn Asn Thr Val Thr Ala Gln Ile Gly  
                   130                  135                  140

Ile Val Ala Val Val Arg Gly Ser Leu Phe Phe Phe Pro Leu Pro Leu  
                   145                  150                  155                  160

Leu Ile Lys Arg Leu Ala Phe Cys His Ser Asn Val Leu Ser His Ser  
                   165                  170                  175

Tyr Cys Val His Gln Asp Val Met Lys Leu Ala Tyr Ala Asp Thr Leu  
                   180                  185                  190

Pro Asn Val Val Tyr Gly Leu Thr Ala Ile Leu Leu Val Met Gly Val  
                   195                  200                  205

Asp Val Met Phe Ile Ser Leu Ser Tyr Phe Leu Ile Ile Arg Thr Val  
                   210                  215                  220

Leu Gln Leu Pro Ser Lys Ser Glu Arg Ala Lys Ala Phe Gly Thr Cys  
                   225                  230                  235                  240

Val Ser His Ile Gly Val Val Leu Ala Phe Tyr Val Pro Leu Ile Gly  
                   245                  250                  255

Leu Ser Val Val His Arg Phe Gly Asn Ser Leu His Pro Ile Val Arg  
                   260                  265                  270

Val Val Met Gly Asp Ile Tyr Leu Leu Leu Pro Pro Val Ile Asn Pro  
275 280 285

Ile Ile Tyr Gly Ala Lys Thr Lys Gln Ile Arg Thr Arg Val Leu Ala  
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<213> Homo Sapien

<400> 528  
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<210> 529  
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<212> DNA  
<213> Homo Sapien

<400> 529  
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<210> 530  
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<212> DNA  
<213> Homo sapiens

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<210> 531  
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 <212> DNA  
 <213> Homo sapiens

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<210> 532  
 <211> 292  
 <212> PRT  
 <213> Homo sapiens

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<400> 532
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Ser Gly Lys Ser Asn Val Gly Thr Ser Gly Asp His Asn Asp Ser Ser
          20                      25                      30

Val Lys Thr Leu Gly Ser Lys Arg Cys Lys Trp Cys Cys His Cys Phe
          35                      40                      45

Pro Cys Cys Arg Gly Ser Gly Lys Ser Asn Val Val Ala Trp Gly Asp
          50                      55                      60

Tyr Asp Asp Ser Ala Phe Met Asp Pro Arg Tyr His Val His Gly Glu
          65                      70                      75                      80

Asp Leu Asp Lys Leu His Arg Ala Ala Trp Trp Gly Lys Val Pro Arg
          85                      90                      95

Lys Asp Leu Ile Val Met Leu Arg Asp Thr Asp Val Asn Lys Arg Asp
          100                     105                     110

Lys Gln Lys Arg Thr Ala Leu His Leu Ala Ser Ala Asn Gly Asn Ser
          115                     120                     125

Glu Val Val Lys Leu Val Leu Asp Arg Arg Cys Gln Leu Asn Val Leu

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130 135 140  
 Asn Asn Lys Lys Arg Thr Ala Leu Thr Lys Ala Val Gln Cys Gln Glu  
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 Asp Glu Cys Ala Leu Met Leu Leu Glu His Gly Thr Asp Pro Asn Ile  
 165 170 175  
 Pro Asp Glu Tyr Gly Asn Thr Thr Leu His Tyr Ala Val Tyr Asn Glu  
 180 185 190  
 Asp Lys Leu Met Ala Lys Ala Leu Leu Leu Tyr Gly Ala Asp Ile Glu  
 195 200 205  
 Ser Lys Asn Lys His Gly Leu Thr Pro Leu Leu Leu Gly Ile His Glu  
 210 215 220  
 Gln Lys Gln Gln Val Val Lys Phe Leu Ile Lys Lys Lys Ala Asn Leu  
 225 230 235 240  
 Asn Ala Leu Asp Arg Tyr Gly Arg Thr Ala Leu Ile Leu Ala Val Cys  
 245 250 255  
 Cys Gly Ser Ala Ser Ile Val Ser Pro Leu Leu Glu Gln Asn Val Asp  
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 Val Ser Ser Gln Asp Leu Glu Arg Arg Pro Glu Ser Met Leu Phe Leu  
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 Val Ile Ile Met  
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<210> 534  
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 <212> PRT  
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&lt;400&gt; 534

Met Tyr Lys Leu Gln Cys Asn Asn Cys Ala Thr Asn Gly Ala Thr Glu  
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Arg Lys Gln Ala Ala Gly Ser Gly Ala Gly Tyr Ala Leu Pro Ser Ala  
                           20                          25                          30

Leu Gln Ser Met Pro Gln Gly Ser Tyr Ala Thr Ala Arg Phe Leu Val  
                           35                          40                          45

Ala Lys Arg Pro Thr Thr Gly His Leu Glu Lys Glu Phe Met Phe His  
                           50                          55                          60

Cys Arg Lys Gln Pro Gly Ser Pro Ser Arg Gly Leu Gly Leu Leu Trp  
                           65                          70                          75                          80

Pro Trp Pro Asp Ile Glu Phe Val Pro Arg Gln Asp Lys Leu Thr Gln  
                           85                          90                          95

Ser Ser Val Leu Val Pro Gln Ile Cys Ala Cys Gln Thr Arg Pro Asn  
                           100                          105                          110

Trp Leu Asn Glu Gln Pro Ala Thr Ser Ala Gly Val Arg Leu Glu Glu  
                           115                          120                          125

Val Asp Gln Pro Pro Thr Leu Pro Ser Gln Gly Ser Gly Trp Pro Cys  
                           130                          135                          140

Ser His Ser Leu Ser Gly Cys His Leu Met Ala Asp Ile Ala Lys Ala  
                           145                          150                          155                          160

Leu Gly Lys Ala Asp Gly Pro Trp Pro Tyr Leu Phe Val Arg Arg Thr  
                           165                          170                          175

Asp Val Pro Cys Pro Ala Ala Ser Glu Val Gly Gly Cys Ala Pro Ser  
                           180                          185                          190

Ser Trp His Thr Leu Ala Glu Val Thr Gly Cys Ser Leu Ser Pro Leu  
                           195                          200                          205

Ser Leu Ala Gln His Ala Gln Ala Ser Val Leu Leu Leu Cys Tyr Lys  
                           210                          215                          220

Trp Ser His Ile Gly Glu Thr Ser Ser His Leu Arg Ser Lys Val Tyr  
                           225                          230                          235                          240

Ala Ala Phe Gly Gly Ser Ser Pro Cys Leu Lys Gly Leu Met Ser Leu  
                           245                          250                          255

Trp Ala Ser Trp Leu Pro Arg Gly Arg Pro  
                           260                          265

&lt;210&gt; 535

&lt;211&gt; 6082

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens



&lt;400&gt; 535

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&lt;400&gt; 537

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Phe Thr Val Arg Pro Gly Glu Leu Leu Ala Val Val Gly Pro Val Gly		
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Leu	Gln	Gly	Phe	Trp	Asp	Lys	Glu	Val	Leu	Arg	Ala	Glu	Asn	Asp	Ala		
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Gln	Lys	Pro	Ser	Leu	Thr	Arg	Ala	Ile	Ile	Lys	Cys	Tyr	Trp	Lys	Ser		
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Tyr	Leu	Val	Leu	Gly	Ile	Phe	Thr	Leu	Ile	Glu	Glu	Ser	Ala	Lys	Val		
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Ile	Gln	Pro	Ile	Phe	Leu	Gly	Lys	Ile	Ile	Asn	Tyr	Phe	Glu	Asn	Tyr		
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Asp	Pro	Met	Asp	Ser	Val	Ala	Leu	Asn	Thr	Ala	Tyr	Ala	Tyr	Ala	Thr		
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Val	Leu	Thr	Phe	Cys	Thr	Leu	Ile	Leu	Ala	Ile	Leu	His	His	Leu	Tyr		
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Phe	Tyr	His	Val	Gln	Cys	Ala	Gly	Met	Arg	Leu	Arg	Val	Ala	Met	Cys		
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His	Met	Ile	Tyr	Arg	Lys	Ala	Leu	Arg	Leu	Ser	Asn	Met	Ala	Met	Gly		
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Lys	Thr	Thr	Thr	Gly	Gln	Ile	Val	Asn	Leu	Leu	Ser	Asn	Asp	Val	Asn		
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Lys	Phe	Asp	Gln	Val	Thr	Val	Phe	Leu	His	Phe	Leu	Trp	Ala	Gly	Pro		
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Leu	Gln	Ala	Ile	Ala	Val	Thr	Ala	Leu	Leu	Trp	Met	Glu	Ile	Gly	Ile		
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Ser	Cys	Leu	Ala	Gly	Met	Ala	Val	Leu	Ile	Ile	Leu	Leu	Pro	Leu	Gln		
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Ser	Cys	Phe	Gly	Lys	Leu	Phe	Ser	Ser	Leu	Arg	Ser	Lys	Thr	Ala	Thr		
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Phe	Thr	Asp	Ala	Arg	Ile	Arg	Thr	Met	Asn	Glu	Val	Ile	Thr	Gly	Ile		
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Arg	Ile	Ile	Lys	Met	Tyr	Ala	Trp	Glu	Lys	Ser	Phe	Ser	Asn	Leu	Ile		
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 Ser Gln Arg Asn Arg Gln Leu Pro Ser Asp Gly Lys Lys Met Val His  
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 Val Gln Asp Phe Thr Ala Phe Trp Asp Lys Ala Ser Glu Thr Pro Thr  
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 Val Gly Pro Val Gly Ala Gly Lys Ser Ser Leu Leu Ser Ala Val Leu  
 405 410 415  
 Gly Glu Leu Ala Pro Ser His Gly Leu Val Ser Val His Gly Arg Ile  
 420 425 430  
 Ala Tyr Val Ser Gln Gln Pro Trp Val Phe Ser Gly Thr Leu Arg Ser  
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 Asn Ile Leu Phe Gly Lys Lys Tyr Glu Lys Glu Arg Tyr Glu Lys Val  
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 Ile Lys Ala Cys Ala Leu Lys Lys Asp Leu Gln Leu Leu Glu Asp Gly  
 465 470 475 480  
 Asp Leu Thr Val Ile Gly Asp Arg Gly Thr Thr Leu Ser Gly Gly Gln  
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 Lys Ala Arg Val Asn Leu Ala Arg Ala Val Tyr Gln Asp Ala Asp Ile  
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 Tyr Leu Leu Asp Asp Pro Leu Ser Ala Val Asp Ala Glu Val Ser Arg  
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 His Leu Phe Glu Leu Cys Ile Cys Gln Ile Leu His Glu Lys Ile Thr  
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 Ile Leu Val Thr His Gln Leu Gln Tyr Leu Lys Ala Ala Ser Gln Ile  
 545 550 555 560  
 Leu Ile Leu Lys Asp Gly Lys Met Val Gln Lys Gly Thr Tyr Thr Glu  
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 Phe Leu Lys Ser Gly Ile Asp Phe Gly Ser Leu Leu Lys Lys Asp Asn  
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 Glu Glu Ser Glu Gln Pro Pro Val Pro Gly Thr Pro Thr Leu Arg Asn  
 595 600 605  
 Arg Thr Phe Ser Glu Ser Ser Val Trp Ser Gln Gln Ser Ser Arg Pro  
 610 615 620

Ser Leu Lys Asp Gly Ala Leu Glu Ser Gln Asp Thr Glu Asn Val Pro  
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 Val Thr Leu Ser Glu Glu Asn Arg Ser Glu Gly Lys Val Gly Phe Gln  
 645 650 655  
 Ala Tyr Lys Asn Tyr Phe Arg Ala Gly Ala His Trp Ile Val Phe Ile  
 660 665 670  
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 675 680 685  
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 725 730 735  
 Ile Ala Arg Ser Leu Leu Val Phe Tyr Val Leu Val Asn Ser Ser Gln  
 740 745 750  
 Thr Leu His Asn Lys Met Phe Glu Ser Ile Leu Lys Ala Pro Val Leu  
 755 760 765  
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 770 775 780  
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 785 790 795 800  
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 820 825 830  
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 Leu Glu Ser Thr Thr Arg Ser Pro Val Phe Ser His Leu Ser Ser Ser  
 850 855 860  
 Leu Gln Gly Leu Trp Thr Ile Arg Ala Tyr Lys Ala Glu Glu Arg Cys  
 865 870 875 880  
 Gln Glu Leu Phe Asp Ala His Gln Asp Leu His Ser Glu Ala Trp Phe  
 885 890 895  
 Leu Phe Leu Thr Thr Ser Arg Trp Phe Ala Val Arg Leu Asp Ala Ile  
 900 905 910  
 Cys Ala Met Phe Val Ile Ile Val Ala Phe Gly Ser Leu Ile Leu Ala  
 915 920 925  
 Lys Thr Leu Asp Ala Gly Gln Val Gly Leu Ala Leu Ser Tyr Ala Leu

930	935	940
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Glu Asn Met Met Ile Ser Val Glu Arg Val Ile Glu Tyr Thr Asp Leu 965 970 975		
Glu Lys Glu Ala Pro Trp Glu Tyr Gln Lys Arg Pro Pro Pro Ala Trp 980 985 990		
Pro His Glu Gly Val Ile Ile Phe Asp Asn Val Asn Phe Met Tyr Ser 995 1000 1005		
Pro Gly Gly Pro Leu Val Leu Lys His Leu Thr Ala Leu Ile Lys Ser 1010 1015 1020		
Gln Glu Lys Val Gly Ile Val Gly Arg Thr Gly Ala Gly Lys Ser Ser 1025 1030 1035 1040		
Leu Ile Ser Ala Leu Phe Arg Leu Ser Glu Pro Glu Gly Lys Ile Trp 1045 1050 1055		
Ile Asp Lys Ile Leu Thr Thr Glu Ile Gly Leu His Asp Leu Arg Lys 1060 1065 1070		
Lys Met Ser Ile Ile Pro Gln Glu Pro Val Leu Phe Thr Gly Thr Met 1075 1080 1085		
Arg Lys Asn Leu Asp Pro Phe Asn Glu His Thr Asp Glu Glu Leu Trp 1090 1095 1100		
Asn Ala Leu Gln Glu Val Gln Leu Lys Glu Thr Ile Glu Asp Leu Pro 1105 1110 1115 1120		
Gly Lys Met Asp Thr Glu Leu Ala Glu Ser Gly Ser Asn Phe Ser Val 1125 1130 1135		
Gly Gln Arg Gln Leu Val Cys Leu Ala Arg Ala Ile Leu Arg Lys Asn 1140 1145 1150		
Gln Ile Leu Ile Ile Asp Glu Ala Thr Ala Asn Val Asp Pro Arg Thr 1155 1160 1165		
Asp Glu Leu Ile Gln Lys Lys Ile Arg Glu Lys Phe Ala His Cys Thr 1170 1175 1180		
Val Leu Thr Ile Ala His Arg Leu Asn Thr Ile Ile Asp Ser Asp Lys 1185 1190 1195 1200		
Ile Met Val Leu Asp Ser Gly Arg Leu Lys Glu Tyr Asp Glu Pro Tyr 1205 1210 1215		
Val Leu Leu Gln Asn Lys Glu Ser Leu Phe Tyr Lys Met Val Gln Gln 1220 1225 1230		
Leu Gly Lys Ala Glu Ala Ala Ala Leu Thr Glu Thr Ala Lys Gln Arg 1235 1240 1245		

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 <213> Artificial Sequence

<220>  
 <223> Made in a lab

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<210> 540  
 <211> 9  
 <212> PRT  
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<220>  
 <223> Made in a lab

<400> 540  
 Ala Val Val Thr Ala Ser Ala Ala Leu  
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<210> 541  
 <211> 14  
 <212> PRT  
 <213> Homo sapiens

<400> 541  
 Leu Ala Gly Leu Leu Cys Pro Asp Pro Arg Pro Leu Glu Leu  
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<210> 542  
 <211> 15  
 <212> PRT  
 <213> Homo sapiens

<400> 542  
 Thr Gln Val Val Phe Asp Lys Ser Asp Leu Ala Lys Tyr Ser Ala  
 5 10 15

<210> 543  
 <211> 12  
 <212> PRT  
 <213> Homo sapiens

<400> 543  
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 5 10

<210> 544  
 <211> 18  
 <212> PRT  
 <213> Homo sapiens

<400> 544  
 Thr Tyr Val Pro Pro Leu Leu Leu Glu Val Gly Val Glu Glu Lys Phe  
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Met Thr

<210> 545  
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 <212> PRT  
 <213> Homo sapiens

<400> 545  
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Ser Val

<210> 546  
 <211> 29  
 <212> PRT  
 <213> Homo sapiens

<400> 546  
 Phe Val Gly Glu Gly Leu Tyr Gln Gly Val Pro Arg Ala Glu Pro Gly  
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<210> 547  
 <211> 58  
 <212> PRT  
 <213> Homo sapiens

<400> 547  
 Val Ala Glu Glu Ala Ala Leu Gly Pro Thr Glu Pro Ala Glu Gly Leu  
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Ala Phe Arg Asn Leu Gly Ala Leu Leu Pro Arg Leu His Gln Leu Cys  
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Cys Arg Met Pro Arg Thr Leu Arg Arg Leu  
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200

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 <211> 18  
 <212> PRT  
 <213> Homo sapiens

<400> 548  
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Glu Cys

<210> 549  
 <211> 18  
 <212> PRT  
 <213> Homo sapiens

<400> 549  
 Leu Glu Ala Leu Leu Ser Asp Leu Phe Arg Asp Pro Asp His Cys Arg  
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Gln Ala

<210> 550  
 <211> 14  
 <212> PRT  
 <213> Homo sapiens

<400> 550  
 Ser Asp His Trp Arg Gly Arg Tyr Gly Arg Arg Arg Pro Phe  
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<210> 551  
 <211> 11  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Made in a lab

<400> 551  
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<210> 552  
 <211> 2577  
 <212> DNA  
 <213> Homo sapiens

<400> 552  
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 tcataccagt ccacggacta ttatgaacca caccacacag gaggaggtga gcactaggca 180  
 agccaaggaa gcttcacctg tacttacagc cacacgccat ggctcatatt acagcctgaa 240

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ctctgectcc actcagatca gtgataacat tagaaactca ttggagcacg aacctgtgtg 300
tgaactgect atccgaagga tctaggttgt gtgcttcgta tgagaatcta atgccagatg 360
atctatcatt gtctcacttt gccccagat aagaccatct agttgcagaa aaataagctc 420
agagcttcca ctgattctac attatggata tgtgccgcg aagcaagcac aaagccctac 480
ttttacacat gcctagtgat gcttcattgga caaggcttgg ctctgttgag tccaactaac 540
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&lt;210&gt; 553

&lt;211&gt; 58

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 553

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Ser Ile Cys Asn Met Thr Cys Ala Ser Val Phe Phe Cys Asp Gln Lys
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Phe Leu Thr Phe Ser Phe Leu Ser Met Val Glu Pro Pro Arg Ala Gly
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Val Leu Asn Ser Gln Ala Thr Asp Ser Tyr Gln Ser Thr Asp Tyr Tyr
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Glu Pro His His Thr Gly Gly Gly Glu His
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<210> 554  
 <211> 59  
 <212> PRT  
 <213> Homo sapiens

<400> 554  
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                   20                  25                  30  
 Met Leu His Gly Gln Gly Leu Ala Leu Leu Ser Pro Thr Asn Leu Pro  
                   35                  40                  45  
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<210> 555  
 <211> 71  
 <212> PRT  
 <213> Homo sapiens

<400> 555  
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 Pro Gln Leu Gly Ala Thr Ala Gln Gly Lys Val His Met Gly Leu Ser  
                   20                  25                  30  
 Thr Ala Gln Gly Ser Ile Gln Asp Ile Lys Val Pro His Ser Ile Asp  
                   35                  40                  45  
 Leu Val Ala Lys Lys Lys Lys Gln Thr Leu Ile Ser Phe Cys His Pro  
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 Ser Asp Pro Leu Glu Leu Leu  
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<210> 556  
 <211> 81  
 <212> PRT  
 <213> Homo sapiens

<400> 556  
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 Ser Pro Arg Thr Ile Met Asn His Thr Thr Gln Glu Glu Val Ser Thr  
                   20                  25                  30  
 Arg Gln Ala Lys Glu Ala Ser Pro Val Leu Thr Ala Thr Arg His Gly  
                   35                  40                  45  
 Ser Tyr Tyr Ser Leu Asn Ser Ala Ser Thr Gln Ile Ser Asp Asn Ile

Ile

<212> PRT

<213> Homo sapiens

<400> 559

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Thr Asn Pro Val Val Asn Cys Leu Ser Glu Gly Ser Arg Leu Cys Ala  
20 25 30

Ser Tyr Glu Asn Leu Met Pro Asp Asp Leu Ser Leu Ser His Phe Ala  
35 40 45

Pro Arg  
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<210> 560

<211> 56

<212> PRT

<213> Homo sapiens

<400> 560

Ile Gly Ser Leu Lys Gly Pro Thr Thr Ala Gly Ser His Cys Ser Gly  
5 10 15

Glu Gly Ser Tyr Gly Thr Phe Tyr Cys Pro Arg Phe Tyr Thr Gly Tyr  
20 25 30

Lys Gly Ala Ser Gln Tyr Arg Ser Gly Ser Lys Glu Glu Glu Thr Asn  
35 40 45

Thr Asp Leu Phe Leu Pro Pro Leu  
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<210> 561

<211> 57

<212> PRT

<213> Homo sapiens

<220>

<221> VARIANT

<222> (1)...(57)

<223> Xaa = Any amino acid

<400> 561

Val Leu His Leu Asp Gln Met Asn Asn Val Gly Ile Xaa Met Asp Lys  
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Gly Leu Lys Ser Pro Glu Ile Lys Asn Pro Ala Pro Thr Gly Thr Ser  
20 25 30

Asn Leu Ser Cys Phe Leu Ser Xaa Phe Trp Leu Met Gln Gly Thr Asn  
35 40 45

Ser Leu Pro Arg Glu Asn Tyr Leu Asn  
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<210> 562  
 <211> 59  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> VARIANT  
 <222> (1)...(59)  
 <223> Xaa = Any amino acid

<400> 562  
 Asp Leu Tyr Pro Xaa Arg Ser Gln His Cys Ser Phe Asp Pro Ser Val  
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                           20                          25                          30  
 Ile Ser Tyr Leu Xaa Leu Glu Met Ser Ser Leu Ser Glu Ser Leu Val  
                           35                          40                          45  
 Leu Ser Ser Gly Asp Tyr Val Leu Asp Thr Pro  
                           50                          55

<210> 563  
 <211> 79  
 <212> PRT  
 <213> Homo sapiens

<400> 563  
 Cys Phe Leu Phe Pro Tyr Leu Trp Leu Tyr Ala Gln Pro Leu Phe Pro  
                           5                          10                          15  
 Lys Gln Gln Pro Pro Ala Leu Ala Pro Gly His Pro Asp Phe Ile His  
                           20                          25                          30  
 Thr Gln Asn Glu Gln Ile Asp Pro Ser Pro His Ile Gln Asn Leu Met  
                           35                          40                          45  
 Trp Asn Pro His Leu Ser Gln Glu Leu Ala Glu Thr Phe Met Val Arg  
                           50                          55                          60  
 Asp Pro Leu Arg Pro Leu Leu Val Phe Ser Leu Ala Asp Ile Arg  
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<210> 564  
 <211> 64  
 <212> PRT  
 <213> Homo sapiens

<400> 564  
 Ala Cys Ser Lys Gly Ser Glu Glu Phe Gln Arg Val Arg Gly Val Ala  
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 Glu Arg Asp Gln Cys Leu Phe Leu Leu Leu Cys Tyr Gln Ile Tyr Thr  
                           20                          25                          30

Val Arg His Leu Tyr Ile Leu Tyr Arg Thr Leu Gly Ser Arg Lys Ser  
           35                          40                          45

His Met Asn Leu Pro Leu Ser Ser Gly Ser Gln Leu Trp Leu Ala Pro  
           50                          55                          60

<210> 565

<211> 57

<212> PRT

<213> Homo sapiens

<220>

<221> VARIANT

<222> (1)...(57)

<223> Xaa = Any amino acid

<400> 565

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Ala Val Cys Cys Gly Ser Ala Ser Ile Val Ser Leu Leu Leu Glu Gln  
                           20                          25                          30

Asn Ile Asp Val Ser Ser Gln Asp Leu Ser Gly Gln Thr Ala Arg Glu  
           35                          40                          45

Tyr Ala Val Ser Ser Xaa His Asn Val  
           50                          55

<210> 566

<211> 55

<212> PRT

<213> Homo sapiens

<400> 566

Ile Leu Leu Glu Phe Phe Arg Asn Gln Arg Gly Ser Leu Asn Pro Arg  
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Lys Thr Val Pro Phe Ile Lys Ser Glu Gly Gly Glu Lys Lys Gly His  
           20                          25                          30

Cys Asn His Ser Val Val Ser Ile Asp Ser Ala Ala Ala Leu Leu Pro  
           35                          40                          45

Leu Lys Leu Val Leu Leu Pro  
           50                          55

<210> 567

<211> 51

<212> PRT

<213> Homo sapiens

<400> 567

Tyr Ser Asp Phe Asp Val Phe Cys Ser His Thr Tyr Gly Tyr Met Leu

207

5 10 15  
 Ser His Cys Ser Gln Ser Ser Ser Pro Leu Leu Trp Pro Leu Gly Ile  
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 Leu Thr Leu Ser Thr His Lys Met Ser Lys Leu Thr Leu Pro Pro Ile  
 35 40 45  
 Phe Arg Thr  
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<210> 568  
 <211> 75  
 <212> PRT  
 <213> Homo sapiens

<400> 568  
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 Tyr Val Ala Phe Asn Ser Val Pro Ser Thr Cys Leu Leu Ala Ser Leu  
 20 25 30  
 Thr Glu Thr Pro Val Thr Thr Ile Leu Thr Ile Ile Ile Asn Leu Thr  
 35 40 45  
 Cys Phe Gln His Ala Glu Ser Ser Tyr Leu Phe Tyr Pro Leu Ala Asp  
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<210> 569  
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 <213> Homo sapiens

<400> 569  
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&lt;210&gt; 570

&lt;211&gt; 951

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 570

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&lt;210&gt; 571

&lt;211&gt; 819

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 571

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&lt;210&gt; 572

&lt;211&gt; 203

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 572

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Arg Glu Arg Val Arg Gly Glu Thr Ala Thr Asn Phe Phe Phe Leu Arg
      20                                25                        30

Gln Glu Ser Gly Pro Val Ala Gln Ala Gly Val Gln Trp His Asp Leu
      35                                40                        45

Ser Ser Leu Gln Pro Leu Pro His Arg Phe Lys Gln Phe Ser Cys Leu
      50                                55                        60

Ser Leu Pro His Ser Trp Asp His Arg Tyr Ala Pro Pro His Leu Ala
      65                                70                        75                        80

Asn Phe Cys Ser Phe Ser Arg Asp Gly Val Ser Leu Cys Cys Ser Gly
      85                                90                        95

Trp Ser Lys Thr Pro Gly Leu Gln Gln Ser Ala Cys Leu Gly Leu Pro
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Lys Cys Trp Gly Tyr Arg His Lys Pro Pro His Pro Ala Cys His Ile
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Leu Leu Asn Tyr
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<400> 574
Met Thr His Ser Ser Ala Trp Leu Glu Arg Pro Gln Glu Thr Tyr Asn
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His Gly Gly Arg Arg Arg Gly Ser Lys Ala Arg Leu Thr Trp Trp Gln
          20                      25                      30

Glu Arg Thr Ser Glu Gly Gly Asp Cys His Lys Leu Phe Phe Phe Glu
          35                      40                      45

Thr Arg Val Trp Pro Cys Cys Pro Gly Trp Ser Ala Val Ala
          50                      55                      60

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<210> 575

<211> 76  
 <212> PRT  
 <213> Homo sapiens

<400> 575  
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 Trp Arg Ala Pro Val Ile Pro Gly Thr Arg Glu Ala Glu Gly Gly Glu  
                           20                          25                          30  
 Ser Leu Glu Pro Gly Arg Leu Arg Glu Glu Asn Arg Leu Asn Pro Gly  
                           35                          40                          45  
 Gly Arg Gly Cys Ser Glu Pro Arg Ser Cys Cys Cys Thr Pro Ala Trp  
                           50                          55                          60  
 Ser Thr Glu Gln Asp Ser Ala Ser Lys Thr Asn Lys  
                           65                          70                          75

<210> 576  
 <211> 68  
 <212> PRT  
 <213> Homo sapiens

<220>  
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 <223> Xaa = Any Amino Acid

<400> 576  
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 Thr Val Cys Tyr Leu Ala Ser Ser Ser Ala Ser Arg Glu Thr Ala Thr  
                           20                          25                          30  
 Arg Gln Ala Pro Gly Asn Trp Lys Met Xaa Ser Lys Cys His Ala Gln  
                           35                          40                          45  
 Leu Leu Phe Thr Phe Tyr Leu Asn His Phe Tyr Gln Ile Arg Leu Asn  
                           50                          55                          60  
 Pro Gly Tyr Ser  
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<210> 577  
 <211> 57  
 <212> PRT  
 <213> Homo sapiens

<400> 577  
 Met Tyr Leu Glu Asn Ser Phe Tyr Cys Gln Met Ile Leu Leu Lys Arg  
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 Cys Arg Leu Ser Lys Ile Ser Thr Gln Arg Val Val Pro Asp Gly Pro



Gly Lys Trp Val Gln Cys Cys Leu Pro Leu Trp Gly Leu Leu Gly Ser  
                   35                                  40                                  45

His Ala Phe Tyr Ile Tyr Ala Val Asp Ile Phe Met Phe Pro Gly Ser  
           50                                  55                                  60

Phe Ile His  
       65

<210> 581

<211> 77

<212> PRT

<213> Homo sapiens

<400> 581

Met Leu Glu Val Lys Phe Glu Val Ser Leu Arg Pro Thr Gly Asn Glu  
                                   5                                  10                                  15

Thr Ala Gly Gln Thr His Gly Thr Gln Asp Lys Gly Ser Lys Asp Ser  
                   20                                  25                                  30

Thr Ala Ala Asp Ile Leu Cys Asp Ser Leu Glu Ser Ser Arg Pro Ala  
                   35                                  40                                  45

Ala His Ile Leu Glu Gly Lys Met Gly Thr Met Leu Ser Ala Thr Leu  
           50                                  55                                  60

Gly Pro Ser Trp Val Thr Cys Ile Leu His Leu Cys Ser  
       65                                  70                                  75

<210> 582

<211> 51

<212> PRT

<213> Homo sapiens

<400> 582

Met Leu Phe Leu Gln Thr Ile Asp Thr Lys Cys Thr Gly Ile Glu Ile  
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Asn Arg Asn Trp Ser Lys Val Trp His Thr His Ser His Val Asp Val  
                   20                                  25                                  30

Lys Leu Cys Leu Glu Phe Leu Cys Gly Val Trp Phe Gly Leu Gly Phe  
                   35                                  40                                  45

Leu Gly Val  
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<210> 583

<211> 60

<212> PRT

<213> Homo sapiens

<400> 583

Met Ser Thr Ser Asp Gly Phe Ala Pro Pro Pro Gln Leu Gly Ser Arg  
5 10 15

Cys Ser His Ile Arg Gly Pro Ile Lys Ile Ala Arg Asn Lys Phe Pro  
20 25 30

Arg Thr Leu Thr Ser Gln Glu Leu Arg Arg Phe Ala Glu Tyr Ser Gly  
35 40 45

Met Met Phe Gly Asp Gln Thr Thr Ala Gly Gln Lys  
50 55 60

<210> 584

<211> 76

<212> PRT

<213> Homo sapiens

<400> 584

Met Cys Leu Cys Ile Pro Leu Gly Gly Tyr Gln Glu Leu Cys His Cys  
5 10 15

Met Ser Thr Ser Asp Gly Phe Ala Pro Pro Pro Gln Leu Gly Ser Arg  
20 25 30

Cys Ser His Ile Arg Gly Pro Ile Lys Ile Ala Arg Asn Lys Phe Pro  
35 40 45

Arg Thr Leu Thr Ser Gln Glu Leu Arg Arg Phe Ala Glu Tyr Ser Gly  
50 55 60

Met Met Phe Gly Asp Gln Thr Thr Ala Gly Gln Lys  
65 70 75

<210> 585

<211> 50

<212> PRT

<213> Homo sapiens

<400> 585

Met Val Tyr Arg Phe Gly Gln Met Ser Asp Asn Pro Phe Tyr Ile Leu  
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Ala Ser Leu Gly Ser Ser Ser Cys Arg Asn Gly Leu Ala Ser Lys Trp  
20 25 30

Arg Gln Ala Asp Pro Ser Asp Gly Tyr Met Glu Pro Cys Phe Gln Leu  
35 40 45

Leu Phe  
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<210> 586

<211> 60

<212> PRT

<213> Homo sapiens

&lt;400&gt; 586

Met Leu Val His Ile Tyr Ser Cys Cys Gly Met Val Tyr Arg Phe Gly  
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Gln Met Ser Asp Asn Pro Phe Tyr Ile Leu Ala Ser Leu Gly Ser Ser  
                   20                  25                  30

Ser Cys Arg Asn Gly Leu Ala Ser Lys Trp Arg Gln Ala Asp Pro Ser  
                   35                  40                  45

Asp Gly Tyr Met Glu Pro Cys Phe Gln Leu Leu Phe  
                   50                  55                  60

&lt;210&gt; 587

&lt;211&gt; 1408

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 587

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&lt;210&gt; 588

&lt;211&gt; 81

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 588

Met Pro Gln Lys Gln Gln Asn Ser Gln Thr Glu Ala Lys Tyr Arg Ala  
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Leu Gln Phe Arg Gln Tyr Asn Lys Ser Val His Glu Val Asn Leu Lys  
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<210> 589
<211> 157
<212> PRT
<213> Homo sapiens
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<210> 590
<211> 347
<212> PRT
<213> Homo sapiens
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<400> 590  
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Ser Leu Ser Asp Cys Gln Thr Pro Thr Gly Trp Asn Cys Ser Gly Tyr  
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 Asp Asp Arg Glu Asn Asp Leu Phe Leu Cys Asp Thr Asn Thr Cys Lys  
                   35                                  40                                  45  
 Phe Asp Gly Glu Cys Leu Arg Ile Gly Asp Thr Val Thr Cys Val Cys  
                   50                                  55                                  60  
 Gln Phe Lys Cys Asn Asn Asp Tyr Val Pro Val Cys Gly Ser Asn Gly  
                   65                                  70                                  75                                  80  
 Glu Ser Tyr Gln Asn Glu Cys Tyr Leu Arg Gln Ala Ala Cys Lys Gln  
                                   85                                  90                                  95  
 Gln Ser Glu Ile Leu Val Val Ser Glu Gly Ser Cys Ala Thr Asp Ala  
                                   100                                  105                                  110  
 Gly Ser Gly Ser Gly Asp Gly Val His Glu Gly Ser Gly Glu Thr Ser  
                   115                                  120                                  125  
 Gln Lys Glu Thr Ser Thr Cys Asp Ile Cys Gln Phe Gly Ala Glu Cys  
                   130                                  135                                  140  
 Asp Glu Asp Ala Glu Asp Val Trp Cys Val Cys Asn Ile Asp Cys Ser  
                   145                                  150                                  155                                  160  
 Gln Thr Asn Phe Asn Pro Leu Cys Ala Ser Asp Gly Lys Ser Tyr Asp  
                                   165                                  170                                  175  
 Asn Ala Cys Gln Ile Lys Glu Ala Ser Cys Gln Lys Gln Glu Lys Ile  
                                   180                                  185                                  190  
 Glu Val Met Ser Leu Gly Arg Cys Gln Asp Asn Thr Thr Thr Thr Thr  
                   195                                  200                                  205  
 Lys Ser Glu Asp Gly His Tyr Ala Arg Thr Asp Tyr Ala Glu Asn Ala  
                   210                                  215                                  220  
 Asn Lys Leu Glu Glu Ser Ala Arg Glu His His Ile Pro Cys Pro Glu  
                   225                                  230                                  235                                  240  
 His Tyr Asn Gly Phe Cys Met His Gly Lys Cys Glu His Ser Ile Asn  
                                   245                                  250                                  255  
 Met Gln Glu Pro Ser Cys Arg Cys Asp Ala Gly Tyr Thr Gly Gln His  
                   260                                  265                                  270  
 Cys Glu Lys Lys Asp Tyr Ser Val Leu Tyr Val Val Pro Gly Pro Val  
                   275                                  280                                  285  
 Arg Phe Gln Tyr Val Leu Ile Ala Ala Val Ile Gly Thr Ile Gln Ile  
                   290                                  295                                  300  
 Ala Val Ile Cys Val Val Val Leu Cys Ile Thr Arg Lys Cys Pro Arg  
                   305                                  310                                  315                                  320



Ser Asn Arg Ile His Arg Gln Lys Gln Asn Thr Gly His Tyr Ser Ser  
 325 330 335

Asp Asn Thr Thr Arg Ala Ser Thr Arg Leu Ile  
 340 345

<210> 591  
 <211> 565  
 <212> DNA  
 <213> Homo sapien

<400> 591  
 actaaagcaa atgaacaagc tgacttgcta gtatcatctg cattcattga agcacaagaa 60  
 cttcatgcct tgactcatgt aaatgcaata ggattaaaaa ataaatttga tatcacatgg 120  
 aaacagacaa aaaatattgt acaacattgc acccagtgtc agattctaca cctggccact 180  
 caggaagcaa gagttaatcc cagaggtcta tgtcctaattg tgttatggca aatggatgtc 240  
 atgcacgtac cttcatttgg aaaattgtca tttgtccatg tgacagttga tacttattca 300  
 catttcatat gggcaacctg ccagacagga gaaagtactt cccatgttaa aagacattta 360  
 ttatcttgtt ttctgtcat gggagttcca gaaaaagtta aaacagacaa tgggccagggt 420  
 tactgtagta aagcatttca aaaattctta aatcagtggg aaattacaca tacaatagga 480  
 attctctata attcccaagg acaggccata attgaaggaa ctaatagaac actcaaagct 540  
 caattggtta aacaaaaaaa aaaaa 565

<210> 592  
 <211> 188  
 <212> PRT  
 <213> Homo sapien

<400> 592  
 Thr Lys Ala Asn Glu Gln Ala Asp Leu Leu Val Ser Ser Ala Phe Ile  
 1 5 10 15  
 Glu Ala Gln Glu Leu His Ala Leu Thr His Val Asn Ala Ile Gly Leu  
 20 25 30  
 Lys Asn Lys Phe Asp Ile Thr Trp Lys Gln Thr Lys Asn Ile Val Gln  
 35 40 45  
 His Cys Thr Gln Cys Gln Ile Leu His Leu Ala Thr Gln Glu Ala Arg  
 50 55 60  
 Val Asn Pro Arg Gly Leu Cys Pro Asn Val Leu Trp Gln Met Asp Val  
 65 70 75 80  
 Met His Val Pro Ser Phe Gly Lys Leu Ser Phe Val His Val Thr Val  
 85 90 95  
 Asp Thr Tyr Ser His Phe Ile Trp Ala Thr Cys Gln Thr Gly Glu Ser  
 100 105 110  
 Thr Ser His Val Lys Arg His Leu Leu Ser Cys Phe Pro Val Met Gly  
 115 120 125  
 Val Pro Glu Lys Val Lys Thr Asp Asn Gly Pro Gly Tyr Cys Ser Lys  
 130 135 140  
 Ala Phe Gln Lys Phe Leu Asn Gln Trp Lys Ile Thr His Thr Ile Gly  
 145 150 155 160  
 Ile Leu Tyr Asn Ser Gln Gly Gln Ala Ile Ile Glu Gly Thr Asn Arg  
 165 170 175  
 Thr Leu Lys Ala Gln Leu Val Lys Gln Lys Lys Lys  
 180 185

<210> 593  
 <211> 271

<212> DNA  
<213> Homo sapien

<220>  
<221> misc\_feature  
<222> (1)...(271)  
<223> n = A,T,C or G

<400> 593  
actttatggt cnagtgcana aancncctg gattgccacc ntactctcag ggctgtgant 60  
tgtgcnccca nagcaacctg ggcaacgagg gacagggggg ccnacaattg agggagcggg 120  
gtccctagct ggggtctata catgncnggg naagggcngc tgagtnccat nagcaaagga 180  
nctagnatnt gcgggggtgc ggctggggc taccctttna agcatcctn gatccactcc 240  
angaanccng gggtagnacg gtttnccaac a 271

<210> 594  
<211> 376  
<212> DNA  
<213> Homo sapien

<220>  
<221> misc\_feature  
<222> (1)...(376)  
<223> n = A,T,C or G

<400> 594  
cctttggggg nggggggaac ctttaccatt gtnecccttt atttcatttg gttnnggggtc 60  
gcgcctcnn ggccaacaa agttatcgtn nttgaagaga anattttttt ggnttngncc 120  
cgattaagcg ncaaattgtgt agcaaaaangc cgtgccactt gtggcgtagc tncgtcgggt 180  
cgattcgacg acaaggcgtg gcgcgntanc gttagtctcn aatngaccn gtggcatgag 240  
cccacgangg ntctgtgtcg tcacatggnc tctagacata acgcncncn ttttttncag 300  
agggggntgc cgcccttagg gaggnagggg tggggacact agccaancca nantctnacc 360  
ccattgaaga aaagg 376

<210> 595  
<211> 242  
<212> DNA  
<213> Homo sapien

<220>  
<221> misc\_feature  
<222> (1)...(242)  
<223> n = A,T,C or G

<400> 595  
agnctgctgn tcgtnccctn tatgtggctt catnntgagg acaanagtng cactgaggct 60  
tgngnatgcc aggcaaggnc aagctggctc aaaaagcatc caccacctc tгнаanggg 120  
atgccangag cangtgcacc agtcccaact angagnccn ggcatgntac atcttcttcc 180  
acccctnaaa ntttngctc caangnccat ttttctttt ctcttaaggg ncnctggct 240  
tc 242

<210> 596  
<211> 535  
<212> DNA  
<213> Homo sapien

<220>  
<221> misc\_feature

&lt;222&gt; (1)...(535)

&lt;223&gt; n = A,T,C or G

&lt;400&gt; 596

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accagttgga tactgctaaa nagatattta tgcagcctca tatgttaagt cgtatatatt 60
gaaagctttt taaatttttt ctttaagaag atttttagatg cttatcactg agtaccagag 120
qatgtaggc tgatgccctt atcaacaaag tcagggactg tggcacacaa ggattgacta 180
ctgcagacac ggcacaaatg ctacctctag agggcctgaa tccccctgcc ctctctgggtg 240
gggagaaggg ctggcagagc cattagcatg ggctccggcc aatcctggcc actttgacac 300
tcttgggtgct gaccaggggt cctggaggaa gggatgaggt gggcagtaga gatgctcagg 360
gnagtggccc ctttccatcc aacttggaa tatttcagta ttttaccacc aattcagcca 420
ttcccttggtg cgtctggctga acatcagccc tgcctcaggt ctcagtttcc cctttgtaaa 480
gggaaagctc tggattcagg gagtgatgaa gaggtcatca tggctctgag aattc 535

```

&lt;210&gt; 597

&lt;211&gt; 257

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; (1)...(257)

&lt;223&gt; n = A,T,C or G

&lt;400&gt; 597

```

tttcnatacc caaaantacc ccatattang accanacatt tgtctnggaa aaattaccat 60
tntntaactt ttgggccacc tgagannaaa tgggtgtaat ncatgataag atggancagn 120
atttctctta agatnngatn agaccccggt tttcacggaa catatccaag naccacaatag 180
gnaacaagcc acggngggag tcacaaacat atattcttta ctctcataat ccgtnncaca 240
naactnttgn acttgac 257

```

&lt;210&gt; 598

&lt;211&gt; 222

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; (1)...(222)

&lt;223&gt; n = A,T,C or G

&lt;400&gt; 598

```

nntggntacc gtcnaaactt ncttgggtac ccgagctcgg atccactagt ccagtgtggt 60
qqaattccat tgtgttgggc tataagctgt aatagtggag nctgtctngg ttcatgtgan 120
nagncctcc gcanncaenc ttgnnacaac ctgtgagnag gcnataaatt attcacataa 180
tcactactgc atgaanctga ctcaaacgca tccacntaca cc 222

```

&lt;210&gt; 599

&lt;211&gt; 238

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; (1)...(238)

&lt;223&gt; n = A,T,C or G

&lt;400&gt; 599

gcatgacatc	ancgatgtnt	ttggnnacct	ganattngct	aaaactngng	natgccgggn	60
atgnaggttt	ggtantgate	tatgcactca	catctcatgg	ggacgtttca	tgtggagtgn	120
tcgacaangt	tgctgnancn	gagaagtgat	gatctcagtt	gaaaggggtca	tgtgaatata	180
cnttacactt	gaaaaagaag	cacattggga	atatcacgaa	acgnccacca	acatcctg	238

&lt;210&gt; 600

&lt;211&gt; 232

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; (1)...(232)

&lt;223&gt; n = A,T,C or G

&lt;400&gt; 600

cgaactatit	agactaccta	ggaaaattat	tttagtatca	gaagaatata	aggggtgtag	60
tactcatcag	agctaaatga	gagcgcttta	aaaatgttag	tttgtcttcc	gccatttcta	120
cagaaaagctg	caatttcagg	ttttcaacct	aatagggtgat	atttaanaaa	aaaaaaaaagc	180
aatcgcaaat	agccccactg	cttttacaaa	tcattttttc	cccaacacaa	tg	232

&lt;210&gt; 601

&lt;211&gt; 547

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; (1)...(547)

&lt;223&gt; n = A,T,C or G

&lt;400&gt; 601

cattgtgttg	gggaaaaaat	gatttgtata	agcagtgggg	ctatttgcga	ttgttttttt	60
tttttcttaa	atatcaccta	ttaggttgaa	aacctgaaat	tgcagctttc	tgtagaaatg	120
gcggaagaca	aactaacatt	tttaaagcgc	tctcatttag	ctctgatgag	tactacaccc	180
ctnatattct	tctgatacta	aaataatttt	cctagtgtag	tctaaacttt	tttaaaaaga	240
catgtaatcc	gcggagttag	taactcaaaa	cgagtgcata	tnggaagtat	cgcagccgtt	300
netggatnaa	attcccagct	tgctngcttg	ctnagccggg	gggcggtnaa	aaaaacatct	360
gcagcccngg	ggnaaaaacc	ttcgattgt	tcttacgtgt	ttacgttatt	ttatttccct	420
nnagcaaggc	gggganttg	ggactcgaaa	tggtacagtt	gggctgggga	tcgcccttgt	480
tacataaaag	ncgtccagaa	gagggacggt	tacaggcngg	ganctccaaa	ggtcagtcce	540
tgccatt						547

&lt;210&gt; 602

&lt;211&gt; 826

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; (1)...(826)

&lt;223&gt; n = A,T,C or G

&lt;400&gt; 602

cggggggnnt	tacgtctctc	tggacgcttt	tattgtacca	gggcgatccc	agcccaactg	60
taccattcga	gtccctactc	ctgccttgct	ctagggaaat	aaaataacgt	aaacacgtaa	120
gaacaatgcg	aaagcgtttt	cttccctagg	ctgcagattg	tcttcttcac	cgccctgct	180
tagctagcta	gctagctggg	aatttaatcc	agaaacggct	tgcgatacct	cctagatgca	240

ctcgttttga	gttacaaact	cgcgggatta	catgtctttt	taaaaaagtt	tagactacac	300
tagggaaaat	tatttttagta	tcagaagaat	atcaggggggt	gtagtactca	tcagagctna	360
atgagagcgc	tttaaaaaatg	ttagttttgtc	tcccgccatt	tctacagaaa	gctgcaattt	420
cagggttttca	ncctaataagg	tgatatntaa	gaaaaaaaaa	acaatcgcan	atagcccact	480
gctttttacaa	atcattttttc	tcttctaggt	atagcctgtc	aggtggccta	atgtattttt	540
gacatctcta	ggaatttttaa	tagaccagaa	atgggtgccca	gagatatgcc	tgcactaatc	600
ttaagtgggg	atztatgtat	ttctcaanca	agtgattaaa	gcaaaactag	gcacgaatga	660
aatcaagatc	tttaggccag	aaatcatgaa	nanttttana	attattttan	gaatctgtgg	720
cttctcttct	taaaatngaa	aaaaaaattg	tttaaacccta	naaggtctga	atacccaagc	780
ncctgaaacn	anagaacaan	gcgggagcac	ccctcccaa	atcccc		826

&lt;210&gt; 603

&lt;211&gt; 817

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; (1)...(817)

&lt;223&gt; n = A,T,C or G

&lt;400&gt; 603

nnangacttt	tgtggtntta	tacaattntt	ttttctattt	ctatgaagag	aaagccacag	60
agtcctaaaa	taattctaaa	actcatcatg	actttcttgc	ctaaaagatc	ttgatttcaa	120
tctgtgcctag	ttttgcttta	atcacttgct	tgagaaatac	ataaatcccc	acttaagatt	180
agtgcaggca	tatctctggc	acccatttct	ggttctatta	aaattcctag	agatgtcaaa	240
aattacatta	ggccacctga	caggctatac	ctagaagaga	aaaaatgatt	tgtaaaaagca	300
gtggggctat	ttgcgattgc	tttttttttt	tcttaaatat	cacctattag	gttgaaaacc	360
tgaaattgca	gctttctgta	gaaatggcgg	aagacaaact	aacattttta	aagcgcctct	420
atthagctct	gatgagtact	acacccctga	tattcttctg	atactaaaat	aattttccta	480
gtgtagtcta	aactttttta	aaaagacatg	taatccgcgg	agtttgtaac	tcaaaacgag	540
tgcactctagg	aggtatcgca	agccgtttct	ggattaaatt	cccagctagc	ttgcttgott	600
agcaggggcg	ggnaaanaag	acatctgcag	cctagggaag	aaaacctttc	gcattgttct	660
tacgtgttta	cgttatttta	tttcttanaa	caaggcngaa	ttgggactcg	aatgggttcag	720
ttgggggtggg	ggatccctcg	gtncataaaa	ngtcanaaag	anggtacagg	cggaaaccca	780
agggctcgtcc	tgcatttana	ctcggaattt	tggtgcc			817

&lt;210&gt; 604

&lt;211&gt; 694

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; (1)...(694)

&lt;223&gt; n = A,T,C or G

&lt;400&gt; 604

cttttcaaat	catttttntc	cttctaggta	tancctgtca	ggtggcctaa	tgtaatTTTT	60
gacatctcta	ngaattttta	tagaaccaga	aatgggtgcc	agagatatgc	ctgcaactaat	120
cttaagtggg	gatttatgta	tttctcaagc	aagtgattaa	agcaaaaacta	ggcacgattg	180
aaatcaagat	cttttaggca	anaaagtcac	gatgagtttt	agaattatTT	taggactctg	240
tggcttttct	ttcatagaaa	tagaaaaaaa	aattgtataa	aaccacaaaa	ggtcctgaat	300
agccaaagca	acactganca	aaaagaacan	agcagggaag	caacacacta	ccngaattca	360
aattatacta	ccagggtgta	gtaacccaaa	cagcattcta	ttggcataaa	atagacacca	420
agaccaatgg	ancagaataa	agaacccccc	aaataaatcc	atataatntac	cgccanctga	480
ttatcaataa	cnaacaccaa	gaacatatnt	taagggaent	nctattccaat	aantagtgtc	540
ggnaaaaaact	gggaaatcca	tatgcagaaa	naatgaaact	agacccctat	ccctcaccat	600

acgcaaannt caacttcgga atgggattac aaaacttaag acattccaac ccaagaaact 660  
atnaaancta ctattaagaa aacagatcnc nccc 694

<210> 605  
<211> 678  
<212> DNA  
<213> Homo sapien

<220>  
<221> misc\_feature  
<222> (1)...(678)  
<223> n = A,T,C or G

<400> 605  
taaaaatcta gactacacta ggaaattatt ttantatcag aagaatatca ggggtgtagt 60  
actcatcana gctaaatgag agcgctttaa aaatgttagt ttgtcttccg ccatttctac 120  
agaaagctgc aatttcaggt tttcaaccta atagggtgata ttttaagaaaa aaaaaaagca 180  
atcgcaata gccccactgc ttttaciaat catTTTTTct ctctaggta tagcctgtca 240  
ggtggcctaa tgtaattttt gacatctcta ggaattttta tagaaccaga aatgggtgcc 300  
agagatatgc ctgcactaat ctttaagtggg gatattatgta tttctcaagc aagtgattaa 360  
agcaaaaacta ggcacgattg aaatcaanat ctttttaggca agaaagtcac gatgagtttt 420  
anaattattt taggactctg tggctttctc ttcatagaaa tagaaaaaaa aaattgtata 480  
aaaaccacaa aaggtcctga atagcccaaa gcaacactga acaaaaangaa caaagcagga 540  
agcaacacac taccggaatt caattatact accaaggtgt antaaccaaa acagcattct 600  
attgggcata aaatagacca aagaccagtg ggaaacagaa taaagaancc caaaataaat 660  
cctatattta cngccnc 678

<210> 606  
<211> 263  
<212> DNA  
<213> Homo sapien

<220>  
<221> misc\_feature  
<222> (1)...(263)  
<223> n = A,T,C or G

<400> 606  
gtgggggtcng cancagccaa ctacagcttcc ttctgggctt tgttagcaga cggatcatcc 60  
tctagtccac tgtgntcaaa ttccattgtg tggggggcnc tcgcctcggc canagatctg 120  
agtgancana cntgtcccca ctgaggtgcc ccacagcngn ttgtnttcag cangggctna 180  
caactcgacc ggcagcgnan ggctggcaga antgngcgcc tnnctcatc ctacgngtn 240  
ngccgcagga aggangacag gcc 263

<210> 607  
<211> 22  
<212> DNA  
<213> Artificial Sequence

<220>  
<223> Primer

<400> 607  
ccatgtgggt cccggttgtc tt 22

<210> 608  
<211> 22  
<212> DNA

<213> Artificial Sequence

<220>

<223> Primer

<400> 608

gctaggggtg ctcaggggtt gg

22

<210> 609

<211> 40

<212> DNA

<213> Artificial Sequence

<220>

<223> Primer

<400> 609

gctggacagg gggcaaaaagc tggggcagtg aacctatgtgc

40

<210> 610

<211> 27

<212> DNA

<213> Artificial Sequence

<220>

<223> Primer

<400> 610

ccttgtccag atagcccagt agctgac

27

<210> 611

<211> 46

<212> DNA

<213> Artificial Sequence

<220>

<223> Primer

<400> 611

gatagagaaa accgtccagg ccagtattgt gggaggctgg gagtgc

46

<210> 612

<211> 40

<212> DNA

<213> Artificial Sequence

<220>

<223> Primer

<400> 612

gcacatgggt cactgcccc gcttttgccc cctgtccagc

40

<210> 613

<211> 38

<212> DNA

<213> Artificial Sequence

<220>

&lt;223&gt; Primer

&lt;400&gt; 613

gccgctcgag ttagaattcg gggttggcca cgatgggtg

38

&lt;210&gt; 614

&lt;211&gt; 53

&lt;212&gt; DNA

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; Primer

&lt;400&gt; 614

cggcgggcat atgcatcacc atcaccatca catcataaac ggcgaggact gca

53

&lt;210&gt; 615

&lt;211&gt; 46

&lt;212&gt; DNA

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; Primer

&lt;400&gt; 615

gcactcccag cctcccacaa tactggcctg gacgggtttc tctatc

46

&lt;210&gt; 616

&lt;211&gt; 1350

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 616

atgcatcacc	atcaccatca	catcataaac	ggcgaggact	gcagcccga	ctcgcagccc	60
tggcaggcgg	cactgggtcat	ggaaaacgaa	ttgttctgct	cgggcgtcct	ggtgcatccg	120
cagtgggtgc	tgtcagccgc	acactgtttc	cagaactcct	acaccatcgg	gctgggcctg	180
cacagtcttg	aggccgacca	agagccaggg	agccagatgg	tggaggccag	cctctccgta	240
cggcaccacg	agtacaacag	acccttgctc	gctaacgacc	tcattgctcat	caagttggac	300
gaatccgtgt	ccgagttctga	caccatccgg	agcatcagca	ttgcttcgca	gtgccctacc	360
gcggggaaact	cttgccctcgt	ttctggctgg	ggtctgctgg	cgaacggcag	aatgcctacc	420
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ccgctgtacc	accccagcat	gttctgcgcc	ggcggagggg	aagaccagaa	ggactcctgc	540
aacggtgact	ctggggggcc	cctgatctgc	aacgggtact	tgcagggcct	tgtgtctttc	600
ggaaaagccc	cgtgtggcca	agttggcgtg	ccagggtgtc	acaccaacct	ctgcaaattc	660
actgagtgga	tagagaaaac	cgtccaggcc	agtattgtgg	gaggtctgga	gtgcgagaag	720
cattcccac	cctggcaggt	gcttgtggcc	tctcgtggca	gggcagtctg	cggcgggtgt	780
ctgggtgcacc	cccagtgggt	cctcacagct	gcccactgca	tcaggaaaca	aagcgtgac	840
ttgctgggtc	ggcacagcct	gtttcatcct	gaagacacag	gccagggtatt	tcaggtcagc	900
cacagcttcc	cacacccgct	ctacgatatg	agcctcctga	agaatcgatt	cctcaggcca	960
ggtgatgact	ccagccacga	cctcatgctg	ctccgcctgt	cagagcctgc	cgagctcacg	1020
gatgctgtga	aggtcatgga	cctgcccacc	caggagccag	cactggggac	cacctgctac	1080
gcctcaggct	ggggcagcat	tgaaccagag	gagttcttga	ccccaaagaa	acttcagtgt	1140
gtggacctcc	atgttatctc	caatgacgtg	tgtgocgaag	ttcacccctca	gaaggtgacc	1200
aagttcatgc	tgtgtgctgg	acgctggaca	gggggcaaaa	gctggggcag	tgaaccatgt	1260
gccctgcccg	aaaggccttc	cctgtacacc	aaggtggtgc	attaccggaa	gtggatcaag	1320
gacaccatcg	tggccaaccc	cgaattctaa				1350

&lt;210&gt; 617



&lt;11&gt; 449

&lt;12&gt; PRT

&lt;13&gt; Homo sapien

&lt;400&gt; 617

```

Met His His His His His His Ile Ile Asn Gly Glu Asp Cys Ser Pro
 1          5          10          15
His Ser Gln Pro Trp Gln Ala Ala Leu Val Met Glu Asn Glu Leu Phe
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Cys Ser Gly Val Leu Val His Pro Gln Trp Val Leu Ser Ala Ala His
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Cys Phe Gln Asn Ser Tyr Thr Ile Gly Leu Gly Leu His Ser Leu Glu
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Arg His Pro Glu Tyr Asn Arg Pro Leu Leu Ala Asn Asp Leu Met Leu
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Ile Lys Leu Asp Glu Ser Val Ser Glu Ser Asp Thr Ile Arg Ser Ile
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Ser Ile Ala Ser Gln Cys Pro Thr Ala Gly Asn Ser Cys Leu Val Ser
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Tyr Leu Gln Gly Leu Val Ser Phe Gly Lys Ala Pro Cys Gly Gln Val
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His Pro Leu Tyr Asp Met Ser Leu Leu Lys Asn Arg Phe Leu Arg Pro
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 <212> DNA  
 <213> Homo sapien

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&lt;211&gt; 3674

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 619

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&lt;210&gt; 620

&lt;211&gt; 2051

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; (1)...(2051)

&lt;223&gt; n = A,T,C or G

&lt;400&gt; 620

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&lt;210&gt; 621

&lt;211&gt; 2841

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; (1)...(2841)

&lt;223&gt; n = A,T,C or G

&lt;400&gt; 621

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&lt;213&gt; Homo sapien

&lt;220&gt;

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&lt;222&gt; (1)...(3228)

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&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 623

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&lt;211&gt; 2904

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 624

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```

&lt;210&gt; 631

&lt;211&gt; 3064

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 631

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&lt;210&gt; 632

&lt;211&gt; 684

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 632

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```

```

Asn Gln Asp Asn Ala Val Ser His His Thr Trp Glu Phe Gln Thr Ser
                20                      25                      30

```

```

Ser Pro Val Phe Arg Arg Gly Gln Val Phe His Leu Arg Leu Val Leu
        35                      40                      45

```

```

Asn Gln Pro Leu Gln Ser Tyr His Gln Leu Lys Leu Glu Phe Ser Thr
    50                      55                      60

```

```

Gly Pro Asn Pro Ser Ile Ala Lys His Thr Leu Val Val Leu Asp Pro
    65                      70                      75                      80

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```

Arg Thr Pro Ser Asp His Tyr Asn Trp Gln Ala Thr Leu Gln Asn Glu
                85                      90                      95

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```

Ser Gly Lys Glu Val Thr Val Ala Val Thr Ser Ser Pro Asn Ala Ile
    100                      105                      110

```

```

Leu Gly Lys Tyr Gln Leu Asn Val Lys Thr Gly Asn His Ile Leu Lys
    115                      120                      125

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```

Ser Glu Glu Asn Ile Leu Tyr Leu Leu Phe Asn Pro Trp Cys Lys Glu
    130                      135                      140

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Asp Met Val Phe Met Pro Asp Glu Asp Glu Arg Lys Glu Tyr Ile Leu
    145                      150                      155                      160

```

```

Asn Asp Thr Gly Cys His Tyr Val Gly Ala Ala Arg Ser Ile Lys Cys
    165                      170                      175

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Lys Pro Trp Asn Phe Gly Gln Phe Glu Lys Asn Val Leu Asp Cys Cys
    180                      185                      190

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```

Ile Ser Leu Leu Thr Glu Ser Ser Leu Lys Pro Thr Asp Arg Arg Asp
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Pro Val Leu Val Cys Arg Ala Met Cys Ala Met Met Ser Phe Glu Lys
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Gly Gln Gly Val Leu Ile Gly Asn Trp Thr Gly Asp Tyr Glu Gly Gly

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Thr Ala Pro Tyr Lys Trp Thr Gly Ser Ala Pro Ile Leu Gln Gln Tyr	245		250		255	
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Gly Ile Leu Thr Thr Val Leu Arg Ala Leu Gly Ile Pro Ala Arg Ser	275		280		285	
Val Thr Gly Phe Asp Ser Ala His Asp Thr Glu Arg Asn Leu Thr Val	290		295		300	
Asp Thr Tyr Val Asn Glu Asn Gly Lys Lys Ile Thr Ser Met Thr His	305		310		315	320
Asp Ser Val Trp Asn Phe His Val Trp Thr Asp Ala Trp Met Lys Arg	325		330		335	
Pro Asp Leu Pro Lys Gly Tyr Asp Gly Trp Gln Ala Val Asp Ala Thr	340		345		350	
Pro Gln Glu Arg Ser Gln Gly Val Phe Cys Cys Gly Pro Ser Pro Leu	355		360		365	
Thr Ala Ile Arg Lys Gly Asp Ile Phe Ile Val Tyr Asp Thr Arg Phe	370		375		380	
Val Phe Ser Glu Val Asn Gly Asp Arg Leu Ile Trp Leu Val Lys Met	385		390		395	400
Val Asn Gly Gln Glu Glu Leu His Val Ile Ser Met Glu Thr Thr Ser	405		410		415	
Ile Gly Lys Asn Ile Ser Thr Lys Ala Val Gly Gln Asp Arg Arg Arg	420		425		430	
Asp Ile Thr Tyr Glu Tyr Lys Tyr Pro Glu Gly Ser Ser Glu Glu Arg	435		440		445	
Gln Val Met Asp His Ala Phe Leu Leu Leu Ser Ser Glu Arg Glu His	450		455		460	
Arg Arg Pro Val Lys Glu Asn Phe Leu His Met Ser Val Gln Ser Asp	465		470		475	480
Asp Val Leu Leu Gly Asn Ser Val Asn Phe Thr Val Ile Leu Lys Arg	485		490		495	
Lys Thr Ala Ala Leu Gln Asn Val Asn Ile Leu Gly Ser Phe Glu Leu	500		505		510	
Gln Leu Tyr Thr Gly Lys Lys Met Ala Lys Leu Cys Asp Leu Asn Lys	515		520		525	
Thr Ser Gln Ile Gln Gly Gln Val Ser Glu Val Thr Leu Thr Leu Asp	530		535		540	

Ser Lys Thr Tyr Ile Asn Ser Leu Ala Ile Leu Asp Asp Glu Pro Val  
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 Ile Arg Gly Phe Ile Ile Ala Glu Ile Val Glu Ser Lys Glu Ile Met  
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 Ala Ser Glu Val Phe Thr Ser Phe Gln Tyr Pro Glu Phe Ser Ile Glu  
 580 585 590  
 Leu Pro Asn Thr Gly Arg Ile Gly Gln Leu Leu Val Cys Asn Cys Ile  
 595 600 605  
 Phe Lys Asn Thr Leu Ala Ile Pro Leu Thr Asp Val Lys Phe Ser Leu  
 610 615 620  
 Glu Ser Leu Gly Ile Ser Ser Leu Gln Thr Ser Asp His Gly Thr Val  
 625 630 635 640  
 Gln Pro Gly Glu Thr Ile Gln Ser Gln Ile Lys Cys Thr Pro Ile Lys  
 645 650 655  
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 Glu Ile Asn Ala Gln Lys Ile Val Leu Ile Thr Lys  
 675 680  
  
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 <211> 679  
 <212> PRT  
 <213> Homo sapiens  
  
 <400> 633  
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 Ser Pro Val Phe Arg Arg Gly Gln Val Phe His Leu Arg Leu Val Leu  
 35 40 45  
 Asn Gln Pro Leu Gln Ser Tyr His Gln Leu Lys Leu Glu Phe Ser Thr  
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 Gly Pro Asn Pro Ser Ile Ala Lys His Thr Leu Val Val Leu Asp Pro  
 65 70 75 80  
 Arg Thr Pro Ser Asp His Tyr Asn Trp Gln Ala Thr Leu Gln Asn Glu  
 85 90 95  
 Ser Gly Lys Glu Val Thr Val Ala Val Thr Ser Ser Pro Asn Ala Ile  
 100 105 110  
 Leu Gly Lys Tyr Gln Leu Asn Val Lys Thr Gly Asn His Ile Leu Lys  
 115 120 125

Ser Glu Glu Asn Ile Leu Tyr Leu Leu Phe Asn Pro Trp Cys Lys Glu  
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 145 150 155 160  
 Asn Asp Thr Gly Cys His Tyr Val Gly Ala Ala Arg Ser Ile Lys Cys  
 165 170 175  
 Lys Pro Trp Asn Phe Gly Gln Phe Glu Lys Asn Val Leu Asp Cys Cys  
 180 185 190  
 Ile Ser Leu Leu Thr Glu Ser Ser Leu Lys Pro Thr Asp Arg Arg Asp  
 195 200 205  
 Pro Val Leu Val Cys Arg Ala Met Cys Ala Met Met Ser Phe Glu Lys  
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 Thr Ala Pro Tyr Lys Trp Thr Gly Ser Ala Pro Ile Leu Gln Gln Tyr  
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 260 265 270  
 Gly Ile Leu Thr Thr Val Leu Arg Ala Leu Gly Ile Pro Ala Arg Ser  
 275 280 285  
 Val Thr Gly Phe Asp Ser Ala His Asp Thr Glu Arg Asn Leu Thr Val  
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 Asp Thr Tyr Val Asn Glu Asn Gly Glu Lys Ile Thr Ser Met Thr His  
 305 310 315 320  
 Asp Ser Val Trp Asn Phe His Val Trp Thr Asp Ala Trp Met Lys Arg  
 325 330 335  
 Pro Tyr Asp Gly Trp Gln Ala Val Asp Ala Thr Pro Gln Glu Arg Ser  
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 355 360 365  
 Gly Asp Ile Phe Ile Val Tyr Asp Thr Arg Phe Val Phe Ser Glu Val  
 370 375 380  
 Asn Gly Asp Arg Leu Ile Trp Leu Val Lys Met Val Asn Gly Gln Glu  
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 Glu Leu His Val Ile Ser Met Glu Thr Thr Ser Ile Gly Lys Asn Ile  
 405 410 415  
 Ser Thr Lys Ala Val Gly Gln Asp Arg Arg Arg Asp Ile Thr Tyr Glu  
 420 425 430  
 Tyr Lys Tyr Pro Glu Gly Ser Ser Glu Glu Arg Gln Val Met Asp His

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Glu Asn Phe Leu His Met Ser Val Gln Ser Asp Asp Val Leu Leu Gly		
465	470	475
Asn Ser Val Asn Phe Thr Val Ile Leu Lys Arg Lys Thr Ala Ala Leu		
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Gln Asn Val Asn Ile Leu Gly Ser Phe Glu Leu Gln Leu Tyr Thr Gly		
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Lys Lys Met Ala Lys Leu Cys Asp Leu Asn Lys Thr Ser Gln Ile Gln		
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Gly Gln Val Ser Glu Val Thr Leu Thr Leu Asp Ser Lys Thr Tyr Ile		
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Asn Ser Leu Ala Ile Leu Asp Asp Glu Pro Val Ile Arg Gly Phe Ile		
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Ile Ala Glu Ile Val Glu Ser Lys Glu Ile Met Ala Ser Glu Val Phe		
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Thr Ser Asn Gln Tyr Pro Glu Phe Ser Ile Glu Leu Pro Asn Thr Gly		
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Arg Ile Gly Gln Leu Leu Val Cys Asn Cys Ile Phe Lys Asn Thr Leu		
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Ala Ile Pro Leu Thr Asp Val Lys Phe Ser Leu Glu Ser Leu Gly Ile		
	610	615
Ser Ser Leu Gln Thr Ser Asp His Gly Thr Val Gln Pro Gly Glu Thr		
	625	630
Ile Gln Ser Gln Ile Lys Cys Thr Pro Ile Lys Thr Gly Pro Lys Lys		
	645	650
Phe Ile Val Lys Leu Ser Ser Lys Gln Val Lys Glu Ile Asn Ala Gln		
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Lys Ile Val Leu Ile Thr Lys		
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&lt;210&gt; 634

&lt;211&gt; 5668

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 634

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&lt;210&gt; 635

&lt;211&gt; 1095

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 635

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Met Arg Asn Arg Arg Asn Asp Thr Leu Asp Ser Thr Arg Thr Leu Tyr
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```

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Ser Ser Ala Ser Arg Ser Thr Asp Leu Ser Tyr Ser Glu Ser Asp Leu
                20                      25                      30

```

```

Val Asn Phe Ile Gln Ala Asn Phe Lys Lys Arg Glu Cys Val Phe Phe
                35                      40                      45

```

```

Thr Lys Asp Ser Lys Ala Thr Glu Asn Val Cys Lys Cys Gly Tyr Ala
                50                      55                      60

```

```

Gln Ser Gln His Met Glu Gly Thr Gln Ile Asn Gln Ser Glu Lys Trp
                65                      70                      75                      80

```

```

Asn Tyr Lys Lys His Thr Lys Glu Phe Pro Thr Asp Ala Phe Gly Asp
                85                      90                      95

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Ile Gln Phe Glu Thr Leu Gly Lys Lys Gly Lys Tyr Ile Arg Leu Ser  
 100 105 110  
 Cys Asp Thr Asp Ala Glu Ile Leu Tyr Glu Leu Leu Thr Gln His Trp  
 115 120 125  
 His Leu Lys Thr Pro Asn Leu Val Ile Ser Val Thr Gly Gly Ala Lys  
 130 135 140  
 Asn Phe Ala Leu Lys Pro Arg Met Arg Lys Ile Phe Ser Arg Leu Ile  
 145 150 155 160  
 Tyr Ile Ala Gln Ser Lys Gly Ala Trp Ile Leu Thr Gly Gly Thr His  
 165 170 175  
 Tyr Gly Leu Thr Lys Tyr Ile Gly Glu Val Val Arg Asp Asn Thr Ile  
 180 185 190  
 Ser Arg Ser Ser Glu Glu Asn Ile Val Ala Ile Gly Ile Ala Ala Trp  
 195 200 205  
 Gly Met Val Ser Asn Arg Asp Thr Leu Ile Arg Asn Cys Asp Ala Glu  
 210 215 220  
 Gly Tyr Phe Leu Ala Gln Tyr Leu Met Asp Asp Phe Thr Arg Asp Pro  
 225 230 235 240  
 Leu Tyr Ile Leu Asp Asn Asn His Thr His Leu Leu Leu Val Asp Asn  
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 Gly Cys His Gly His Pro Thr Val Glu Ala Lys Leu Arg Asn Gln Leu  
 260 265 270  
 Glu Lys His Ile Ser Glu Arg Thr Ile Gln Asp Ser Asn Tyr Gly Gly  
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 Lys Ile Pro Ile Val Cys Phe Ala Gln Gly Gly Gly Lys Glu Thr Leu  
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 Lys Ala Ile Asn Thr Ser Ile Lys Asn Lys Ile Pro Cys Val Val Val  
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 Glu Gly Ser Gly Arg Ile Ala Asp Val Ile Ala Ser Leu Val Glu Val  
 325 330 335  
 Glu Asp Ala Pro Thr Ser Ser Ala Val Lys Glu Lys Leu Val Arg Phe  
 340 345 350  
 Leu Pro Arg Thr Val Ser Arg Leu Ser Glu Glu Glu Thr Glu Ser Trp  
 355 360 365  
 Ile Lys Trp Leu Lys Glu Ile Leu Glu Cys Ser His Leu Leu Thr Val  
 370 375 380  
 Ile Lys Met Glu Glu Ala Gly Asp Glu Ile Val Ser Asn Ala Ile Ser  
 385 390 395 400

Tyr Ala Leu Tyr Lys Ala Phe Ser Thr Ser Glu Gln Asp Lys Asp Asn  
 405 410 415  
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 Ala Asn Asp Glu Ile Phe Thr Asn Asp Arg Arg Trp Glu Ser Ala Asp  
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 Leu Gln Glu Val Met Phe Thr Ala Leu Ile Lys Asp Arg Pro Lys Phe  
 450 455 460  
 Val Arg Leu Phe Leu Glu Asn Gly Leu Asn Leu Arg Lys Phe Leu Thr  
 465 470 475 480  
 His Asp Val Leu Thr Glu Leu Phe Ser Asn His Phe Ser Thr Leu Val  
 485 490 495  
 Tyr Arg Asn Leu Gln Ile Ala Lys Asn Ser Tyr Asn Asp Ala Leu Leu  
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 Thr Phe Val Trp Lys Leu Val Ala Asn Phe Arg Arg Gly Phe Arg Lys  
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 Glu Asp Arg Asn Gly Arg Asp Glu Met Asp Ile Glu Leu His Asp Val  
 530 535 540  
 Ser Pro Ile Thr Arg His Pro Leu Gln Ala Leu Phe Ile Trp Ala Ile  
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 Gly Cys Thr Leu Ala Ala Leu Gly Ala Ser Lys Leu Leu Lys Thr Leu  
 580 585 590  
 Ala Lys Val Lys Asn Asp Ile Asn Ala Ala Gly Glu Ser Glu Glu Leu  
 595 600 605  
 Ala Asn Glu Tyr Glu Thr Arg Ala Val Glu Leu Phe Thr Glu Cys Tyr  
 610 615 620  
 Ser Ser Asp Glu Asp Leu Ala Glu Gln Leu Leu Val Tyr Ser Cys Glu  
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 Gln His Phe Thr Ala Gln Pro Gly Val Gln Asn Phe Leu Ser Lys Gln  
 660 665 670  
 Trp Tyr Gly Glu Ile Ser Arg Asp Thr Lys Asn Trp Lys Ile Ile Leu  
 675 680 685  
 Cys Leu Phe Ile Ile Pro Leu Val Gly Cys Gly Phe Val Ser Phe Arg  
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 Lys Lys Pro Val Asp Lys His Lys Lys Leu Leu Trp Tyr Tyr Val Ala

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	725		730		735	
Ile Ala Phe Leu	Leu Leu Phe Ala Tyr Val	Leu Leu Met Asp Phe His				
	740	745		750		
Ser Val Pro His	Pro Pro Glu Leu Val	Leu Tyr Ser Leu Val Phe Val				
	755	760		765		
Leu Phe Cys Asp	Glu Val Arg Gln Trp Tyr Val	Asn Gly Val Asn Tyr				
	770	775		780		
Phe Thr Asp Leu	Trp Asn Val Met Asp Thr	Leu Gly Leu Phe Tyr Phe				
	785	790		795		800
Ile Ala Gly Ile	Val Phe Arg Leu His Ser Ser	Asn Lys Ser Ser Leu				
	805	810			815	
Tyr Ser Gly Arg	Val Ile Phe Cys Leu Asp Tyr Ile	Ile Phe Thr Leu				
	820	825		830		
Arg Leu Ile His	Ile Phe Thr Val Ser Arg Asn Leu	Gly Pro Lys Ile				
	835	840		845		
Ile Met Leu Gln	Arg Met Leu Ile Asp Val Phe Phe	Phe Leu Phe Leu				
	850	855		860		
Phe Ala Val Trp	Met Val Ala Phe Gly Val Ala Arg	Gln Gly Ile Leu				
	865	870		875		880
Arg Gln Asn Glu	Gln Arg Trp Arg Trp Ile Phe Arg	Ser Val Ile Tyr				
	885	890		895		
Glu Pro Tyr Leu	Ala Met Phe Gly Gln Val Pro Ser Asp	Val Asp Gly				
	900	905		910		
Thr Thr Tyr Asp	Phe Ala His Cys Thr Phe Thr Gly	Asn Glu Ser Lys				
	915	920		925		
Pro Leu Cys Val	Glu Leu Asp Glu His Asn Leu Pro Arg	Phe Pro Glu				
	930	935		940		
Trp Ile Thr Ile	Pro Leu Val Cys Ile Tyr Met Leu Ser	Thr Asn Ile				
	945	950		955		960
Leu Leu Val Asn	Leu Leu Val Ala Met Phe Gly Tyr Thr	Val Gly Thr				
	965	970		975		
Val Gln Glu Asn	Asn Asp Gln Val Trp Lys Phe Gln Arg	Tyr Phe Leu				
	980	985		990		
Val Gln Glu Tyr	Cys Ser Arg Leu Asn Ile Pro Phe Pro	Phe Ile Val				
	995	1000		1005		
Phe Ala Tyr Phe	Tyr Met Val Val Lys Lys Cys Phe Lys	Cys Cys Cys				
	1010	1015		1020		

Lys Glu Lys Asn Met Glu Ser Ser Val Cys Cys Phe Lys Asn Glu Asp  
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Asn Glu Thr Leu Ala Trp Glu Gly Val Met Lys Glu Asn Tyr Leu Val  
 1045 1050 1055

Lys Ile Asn Thr Lys Ala Asn Asp Thr Ser Glu Glu Met Arg His Arg  
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Phe Arg Gln Leu Asp Thr Lys Leu Asn Asp Leu Lys Gly Leu Leu Lys  
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Glu Ile Ala Asn Lys Ile Lys  
 1090 1095

<210> 636

<211> 3639

<212> DNA

<213> Homo sapiens

<400> 636

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agcatgagga acagaaggaa tgacactctg gacagcacc ggaccctgta ctccagcgcg 180
tctcggagca cagacttgct ttacagtga agcgacttgg tgaattttat tcaagcaaat 240
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aagtgtggct atgcccagag ccagcacatg gaaggcacc agatcaacca aagtgaagaa 360
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&lt;210&gt; 637

&lt;211&gt; 1095

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; VARIANT

&lt;222&gt; (1)...(1095)

&lt;223&gt; Xaa = Any Amino Acid

&lt;400&gt; 637

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Met Arg Asn Arg Arg Asn Asp Thr Leu Asp Ser Thr Arg Thr Leu Tyr
          5                                10                            15

```

```

Ser Ser Ala Ser Arg Ser Thr Asp Leu Ser Tyr Ser Glu Ser Asp Leu
          20                                25                            30

```

```

Val Asn Phe Ile Gln Ala Asn Phe Lys Lys Arg Glu Cys Val Phe Phe
          35                                40                            45

```

```

Thr Lys Asp Ser Lys Ala Thr Glu Asn Val Cys Lys Cys Gly Tyr Ala
          50                                55                            60

```

```

Gln Ser Gln His Met Glu Gly Thr Gln Ile Asn Gln Ser Glu Lys Trp
          65                                70                            75                            80

```

```

Asn Tyr Lys Lys His Thr Lys Glu Phe Pro Thr Asp Ala Phe Gly Asp
          85                                90                            95

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```

Ile Gln Phe Glu Thr Leu Gly Lys Lys Gly Lys Tyr Ile Arg Leu Ser

```

100	105	110
Cys Asp Thr Asp Ala Glu Ile Leu Tyr Glu Leu Leu Thr Gln His Trp 115	120	125
His Leu Lys Thr Pro Asn Leu Val Ile Ser Val Thr Gly Gly Ala Lys 130	135	140
Asn Phe Ala Leu Lys Pro Arg Met Arg Lys Ile Phe Ser Arg Leu Ile 145	150	155 160
Tyr Ile Ala Gln Ser Lys Gly Ala Trp Ile Leu Thr Gly Gly Thr His 165	170	175
Tyr Gly Leu Met Lys Tyr Ile Gly Glu Val Val Arg Asp Asn Thr Ile 180	185	190
Ser Arg Ser Ser Glu Glu Asn Ile Val Ala Ile Gly Ile Ala Ala Trp 195	200	205
Gly Met Val Ser Asn Arg Asp Thr Leu Ile Arg Asn Cys Asp Ala Glu 210	215	220
Gly Tyr Phe Leu Ala Gln Tyr Leu Met Asp Asp Phe Thr Arg Asp Pro 225	230	235 240
Leu Tyr Ile Leu Asp Asn Asn His Thr His Leu Leu Leu Val Asp Asn 245	250	255
Gly Cys His Gly His Pro Thr Val Glu Ala Lys Leu Arg Asn Gln Leu 260	265	270
Glu Lys Tyr Ile Ser Glu Arg Thr Ile Gln Asp Ser Asn Tyr Gly Gly 275	280	285
Lys Ile Pro Ile Val Cys Phe Ala Gln Gly Gly Gly Lys Glu Thr Leu 290	295	300
Lys Ala Ile Asn Thr Ser Ile Lys Asn Lys Ile Pro Cys Val Val Val 305	310	315 320
Glu Gly Ser Gly Gln Ile Ala Asp Val Ile Ala Ser Leu Val Glu Val 325	330	335
Glu Asp Ala Leu Thr Ser Ser Ala Val Lys Glu Lys Leu Val Arg Phe 340	345	350
Leu Pro Arg Thr Val Ser Arg Leu Pro Glu Glu Glu Thr Glu Ser Trp 355	360	365
Ile Lys Trp Leu Lys Glu Ile Leu Glu Cys Ser His Leu Leu Thr Val 370	375	380
Ile Lys Met Glu Glu Ala Gly Asp Glu Ile Val Ser Asn Ala Ile Ser 385	390	395 400
Tyr Ala Leu Tyr Lys Ala Phe Ser Thr Ser Glu Gln Asp Lys Asp Asn 405	410	415

Trp Asn Gly Gln Leu Lys Leu Leu Leu Glu Trp Asn Gln Leu Asp Leu  
 420 425 430  
 Ala Asn Asp Glu Ile Phe Thr Asn Asp Arg Arg Trp Glu Ser Ala Asp  
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 Leu Gln Glu Val Met Phe Thr Ala Leu Ile Lys Asp Arg Pro Lys Phe  
 450 455 460  
 Val Arg Leu Phe Leu Glu Asn Gly Leu Asn Leu Arg Lys Phe Leu Thr  
 465 470 475 480  
 His Asp Val Leu Thr Glu Leu Phe Ser Asn His Phe Ser Thr Leu Val  
 485 490 495  
 Tyr Arg Asn Leu Gln Ile Ala Lys Asn Ser Tyr Asn Asp Ala Leu Leu  
 500 505 510  
 Thr Phe Val Trp Lys Leu Val Ala Asn Phe Arg Arg Gly Phe Arg Lys  
 515 520 525  
 Glu Asp Arg Asn Gly Arg Asp Glu Met Asp Ile Glu Leu His Asp Val  
 530 535 540  
 Ser Pro Ile Thr Arg His Pro Leu Gln Ala Leu Phe Ile Trp Ala Ile  
 545 550 555 560  
 Leu Gln Asn Lys Lys Glu Leu Ser Lys Val Ile Trp Glu Gln Thr Arg  
 565 570 575  
 Gly Cys Thr Leu Ala Ala Leu Gly Ala Ser Lys Leu Leu Lys Thr Leu  
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 Ala Lys Val Lys Asn Asp Ile Asn Ala Ala Gly Glu Ser Glu Glu Leu  
 595 600 605  
 Ala Asn Glu Tyr Glu Thr Arg Ala Val Glu Leu Phe Thr Glu Cys Tyr  
 610 615 620  
 Ser Ser Asp Glu Asp Leu Ala Glu Gln Leu Leu Val Tyr Ser Cys Glu  
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 645 650 655  
 Gln His Phe Ile Ala Gln Pro Gly Val Gln Asn Phe Leu Ser Lys Gln  
 660 665 670  
 Trp Tyr Gly Glu Ile Ser Arg Asp Thr Lys Asn Trp Lys Ile Ile Leu  
 675 680 685  
 Cys Leu Phe Ile Ile Pro Leu Val Gly Cys Gly Phe Val Ser Phe Arg  
 690 695 700  
 Lys Lys Pro Val Asp Lys His Lys Lys Leu Leu Trp Tyr Tyr Val Ala  
 705 710 715 720

Phe Phe Thr Ser Pro Phe Val Val Phe Ser Trp Asn Val Val Phe Tyr  
                     725                    730                    735  
 Ile Ala Phe Leu Leu Leu Phe Ala Tyr Val Leu Leu Met Asp Phe His  
                     740                    745                    750  
 Ser Val Pro His Pro Pro Glu Leu Val Leu Tyr Ser Leu Val Phe Val  
                     755                    760                    765  
 Leu Phe Cys Asp Glu Val Arg Gln Trp Tyr Val Asn Gly Val Asn Tyr  
                     770                    775                    780  
 Phe Thr Asp Leu Trp Asn Val Met Asp Thr Leu Gly Leu Phe Tyr Phe  
                     785                    790                    795                    800  
 Ile Ala Gly Ile Val Phe Arg Leu His Ser Ser Asn Lys Ser Ser Leu  
                     805                    810                    815  
 Tyr Ser Gly Arg Val Ile Phe Cys Leu Asp Tyr Ile Ile Phe Thr Leu  
                     820                    825                    830  
 Arg Leu Ile His Ile Phe Thr Val Ser Arg Asn Leu Gly Pro Lys Ile  
                     835                    840                    845  
 Ile Met Leu Gln Arg Met Leu Ile Asp Val Phe Phe Phe Leu Phe Leu  
                     850                    855                    860  
 Phe Ala Xaa Trp Met Val Ala Phe Gly Val Ala Arg Gln Gly Ile Leu  
                     865                    870                    875                    880  
 Arg Gln Asn Glu Gln Arg Trp Arg Trp Ile Phe Arg Ser Val Ile Tyr  
                     885                    890                    895  
 Glu Pro Tyr Leu Ala Met Phe Gly Gln Val Pro Ser Asp Val Asp Gly  
                     900                    905                    910  
 Thr Thr Tyr Asp Phe Ala His Cys Thr Phe Thr Gly Asn Glu Ser Lys  
                     915                    920                    925  
 Pro Leu Cys Val Glu Leu Asp Glu His Asn Leu Pro Arg Phe Pro Glu  
                     930                    935                    940  
 Trp Ile Thr Ile Pro Leu Val Cys Ile Tyr Met Leu Ser Thr Asn Ile  
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 Leu Leu Val Asn Leu Leu Val Ala Met Phe Gly Tyr Thr Val Gly Thr  
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 Val Gln Glu Asn Asn Asp Gln Val Trp Lys Phe Gln Arg Tyr Phe Leu  
                     980                    985                    990  
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                     995                    1000                    1005  
 Phe Ala Tyr Phe Tyr Met Val Val Lys Lys Cys Phe Lys Cys Cys Cys  
                     1010                    1015                    1020  
 Lys Glu Lys Asn Met Glu Ser Ser Val Cys Cys Phe Lys Asn Glu Asp



1025	1030	1035	1040
Asn Glu Thr Leu Ala Trp Glu Gly Val Met Lys Glu Asn Tyr Leu Val			
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Lys Ile Asn Thr Lys Ala Asn Asp Thr Ser Glu Glu Met Arg His Arg			
1060	1065		1070
Phe Arg Gln Leu Asp Thr Lys Leu Asn Asp Leu Lys Gly Leu Leu Lys			
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Glu Ile Ala Asn Lys Ile Lys			
1090	1095		

<210> 638  
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 <212> PRT  
 <213> Homo sapiens

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                   5                                  10                                  15

<210> 639  
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 <212> DNA  
 <213> Homo sapiens

<400> 639  
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<210> 640  
 <211> 45  
 <212> DNA  
 <213> Homo sapiens

<400> 640  
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<210> 641  
 <211> 45  
 <212> DNA  
 <213> Homo sapiens

<400> 641  
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<210> 642  
 <211> 45  
 <212> DNA  
 <213> Homo sapiens

<400> 642  
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<210> 643  
<211> 45  
<212> DNA  
<213> Homo sapiens

<400> 643  
tacaccatcg ggctgggcct gcacagtctt gaggccgacc aagag

45

<210> 644  
<211> 42  
<212> DNA  
<213> Homo sapiens

<400> 644  
ttccagaact cctacaccat cgggctgggc ctgcacagtc tt

42

<210> 645  
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<212> DNA  
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ctgtcagccg cacactgttt ccagaactcc tacaccatcg ggctg

45

<210> 646  
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<212> DNA  
<213> Homo sapiens

<400> 646  
catccgcagt ggggtgctgtc agccgcacac tgtttccaga actcc

45

<210> 647  
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<212> DNA  
<213> Homo sapiens

<400> 647  
tcgggctgcc tgggtgcatcc gcagtgggtg ctgtcagccg cacac

45

<210> 648  
<211> 45  
<212> DNA  
<213> Homo sapiens

<400> 648  
aacgaattgt tctgctcggg cgtcctgggtg catccgcagt ggggtg

45

<210> 649  
<211> 45  
<212> DNA  
<213> Homo sapiens

<400> 649  
gcactggtca tggaaaacga attgttctgc tcgggctgcc tgggtg

45

<210> 650  
<211> 51

<212> DNA  
<213> Homo sapiens

<400> 650  
tcgcagccct ggcaggcggc actgggtcatg gaaaacgaat tgttctgctc g 51

<210> 651  
<211> 45  
<212> DNA  
<213> Homo sapiens

<400> 651  
atcagcattg cttcgcagtg ccctaccgag gggaactctt gcttc 45

<210> 652  
<211> 45  
<212> DNA  
<213> Homo sapiens

<400> 652  
tccgtgtccg agtctgacac catccggagc atcagcattg cttcg 45

<210> 653  
<211> 45  
<212> DNA  
<213> Homo sapiens

<400> 653  
atcaagttgg acgaatccgt gtcgagttct gacaccatcc ggagc 45

<210> 654  
<211> 45  
<212> DNA  
<213> Homo sapiens

<400> 654  
aacgacctca tgctcatcaa gttggacgaa tccgtgtccg agtct 45

<210> 655  
<211> 45  
<212> DNA  
<213> Homo sapiens

<400> 655  
agacccttgc tcgctaacga cctcatgctc atcaagttgg acgaa 45

<210> 656  
<211> 15  
<212> PRT  
<213> Homo sapiens

<400> 656  
Glu Pro Gly Ser Gln Met Val Glu Ala Ser Leu Ser Val Arg His  
5 10 15

<210> 657  
<211> 15

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 657

Glu Ala Asp Gln Glu Pro Gly Ser Gln Met Val Glu Ala Ser Leu  
5 10 15

&lt;210&gt; 658

&lt;211&gt; 15

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 658

Gly Leu His Ser Leu Glu Ala Asp Gln Glu Pro Gly Ser Gln Met  
5 10 15

&lt;210&gt; 659

&lt;211&gt; 15

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 659

Tyr Thr Ile Gly Leu Gly Leu His Ser Leu Glu Ala Asp Gln Glu  
5 10 15

&lt;210&gt; 660

&lt;211&gt; 14

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 660

Phe Gln Asn Ser Tyr Thr Ile Gly Leu Gly Leu His Ser Leu  
5 10

&lt;210&gt; 661

&lt;211&gt; 15

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 661

Leu Ser Ala Ala His Cys Phe Gln Asn Ser Tyr Thr Ile Gly Leu  
5 10 15

&lt;210&gt; 662

&lt;211&gt; 15

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 662

His Pro Gln Trp Val Leu Ser Ala Ala His Cys Phe Gln Asn Ser  
5 10 15

<210> 663  
 <211> 15  
 <212> PRT  
 <213> Homo sapiens

<400> 663  
 Ser Gly Val Leu Val His Pro Gln Trp Val Leu Ser Ala Ala His  
                   5                                  10                                  15

<210> 664  
 <211> 15  
 <212> PRT  
 <213> Homo sapiens

<400> 664  
 Asn Glu Leu Phe Cys Ser Gly Val Leu Val His Pro Gln Trp Val  
                   5                                  10                                  15

<210> 665  
 <211> 15  
 <212> PRT  
 <213> Homo sapiens

<400> 665  
 Ala Leu Val Met Glu Asn Glu Leu Phe Cys Ser Gly Val Leu Val  
                   5                                  10                                  15

<210> 666  
 <211> 17  
 <212> PRT  
 <213> Homo sapiens

<400> 666  
 Ser Gln Pro Trp Gln Ala Ala Leu Val Met Glu Asn Glu Leu Phe Cys  
                   5                                  10                                  15

Ser

<210> 667  
 <211> 15  
 <212> PRT  
 <213> Homo sapiens

<400> 667  
 Ile Ser Ile Ala Ser Gln Cys Pro Thr Ala Gly Asn Ser Cys Leu  
                   5                                  10                                  15

<210> 668  
 <211> 15  
 <212> PRT  
 <213> Homo sapiens

&lt;400&gt; 668

Ser Val Ser Glu Ser Asp Thr Ile Arg Ser Ile Ser Ile Ala Ser  
5 10 15

&lt;210&gt; 669

&lt;211&gt; 15

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 669

Ile Lys Leu Asp Glu Ser Val Ser Glu Ser Asp Thr Ile Arg Ser  
5 10 15

&lt;210&gt; 670

&lt;211&gt; 15

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 670

Asn Asp Leu Met Leu Ile Lys Leu Asp Glu Ser Val Ser Glu Ser  
5 10 15

&lt;210&gt; 671

&lt;211&gt; 15

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 671

Arg Pro Leu Leu Ala Asn Asp Leu Met Leu Ile Lys Leu Asp Glu  
5 10 15

&lt;210&gt; 672

&lt;211&gt; 35

&lt;212&gt; DNA

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; PCR primer

&lt;400&gt; 672

ggaccagcat atgaggaaca gaaggaatga cactc

35

&lt;210&gt; 673

&lt;211&gt; 29

&lt;212&gt; DNA

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; PCR primer

&lt;400&gt; 673

ccgctcgagt ccacccaag cttcacagg

29

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<210> 675
<211> 652
<212> PRT
<213> Homo sapiens
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<400> 675
Met Arg Asn Arg Arg Asn Asp Thr Leu Asp Ser Thr Arg Thr Leu Tyr
          5                      10                      15

Ser Ser Ala Ser Arg Ser Thr Asp Leu Ser Tyr Ser Glu Ser Asp Leu
          20                      25                      30

Val Asn Phe Ile Gln Ala Asn Phe Lys Lys Arg Glu Cys Val Phe Phe
          35                      40                      45

Thr Lys Asp Ser Lys Ala Thr Glu Asn Val Cys Lys Cys Gly Tyr Ala
          50                      55                      60

```

Gln Ser Gln His Met Glu Gly Thr Gln Ile Asn Gln Ser Glu Lys Trp  
 65 70 75 80  
 Asn Tyr Lys Lys His Thr Lys Glu Phe Pro Thr Asp Ala Phe Gly Asp  
 85 90 95  
 Ile Gln Phe Glu Thr Leu Gly Lys Lys Gly Lys Tyr Ile Arg Leu Ser  
 100 105 110  
 Cys Asp Thr Asp Ala Glu Ile Leu Tyr Glu Leu Leu Thr Gln His Trp  
 115 120 125  
 His Leu Lys Thr Pro Asn Leu Val Ile Ser Val Thr Gly Gly Ala Lys  
 130 135 140  
 Asn Phe Ala Leu Lys Pro Arg Met Arg Lys Ile Phe Ser Arg Leu Ile  
 145 150 155 160  
 Tyr Ile Ala Gln Ser Lys Gly Ala Trp Ile Leu Thr Gly Gly Thr His  
 165 170 175  
 Tyr Gly Leu Met Lys Tyr Ile Gly Glu Val Val Arg Asp Asn Thr Ile  
 180 185 190  
 Ser Arg Ser Ser Glu Glu Asn Ile Val Ala Ile Gly Ile Ala Ala Trp  
 195 200 205  
 Gly Met Val Ser Asn Arg Asp Thr Leu Ile Arg Asn Cys Asp Ala Glu  
 210 215 220  
 Gly Tyr Phe Leu Ala Gln Tyr Leu Met Asp Asp Phe Thr Arg Asp Pro  
 225 230 235 240  
 Leu Tyr Ile Leu Asp Asn Asn His Thr His Leu Leu Leu Val Asp Asn  
 245 250 255  
 Gly Cys His Gly His Pro Thr Val Glu Ala Lys Leu Arg Asn Gln Leu  
 260 265 270  
 Glu Lys Tyr Ile Ser Glu Arg Thr Ile Gln Asp Ser Asn Tyr Gly Gly  
 275 280 285  
 Lys Ile Pro Ile Val Cys Phe Ala Gln Gly Gly Gly Lys Glu Thr Leu  
 290 295 300  
 Lys Ala Ile Asn Thr Ser Ile Lys Asn Lys Ile Pro Cys Val Val Val  
 305 310 315 320  
 Glu Gly Ser Gly Gln Ile Ala Asp Val Ile Ala Ser Leu Val Glu Val  
 325 330 335  
 Glu Asp Ala Leu Thr Ser Ser Ala Val Lys Glu Lys Leu Val Arg Phe  
 340 345 350  
 Leu Pro Arg Thr Val Ser Arg Leu Pro Glu Glu Glu Thr Glu Ser Trp  
 355 360 365  
 Ile Lys Trp Leu Lys Glu Ile Leu Glu Cys Ser His Leu Leu Thr Val



370	375	380
Ile Lys Met Glu Glu Ala Gly Asp Glu Ile Val Ser Asn Ala Ile Ser 385 390 395 400		
Tyr Ala Leu Tyr Lys Ala Phe Ser Thr Ser Glu Gln Asp Lys Asp Asn 405 410 415		
Trp Asn Gly Gln Leu Lys Leu Leu Leu Glu Trp Asn Gln Leu Asp Leu 420 425 430		
Ala Asn Asp Glu Ile Phe Thr Asn Asp Arg Arg Trp Glu Ser Ala Asp 435 440 445		
Leu Gln Glu Val Met Phe Thr Ala Leu Ile Lys Asp Arg Pro Lys Phe 450 455 460		
Val Arg Leu Phe Leu Glu Asn Gly Leu Asn Leu Arg Lys Phe Leu Thr 465 470 475 480		
His Asp Val Leu Thr Glu Leu Phe Ser Asn His Phe Ser Thr Leu Val 485 490 495		
Tyr Arg Asn Leu Gln Ile Ala Lys Asn Ser Tyr Asn Asp Ala Leu Leu 500 505 510		
Thr Phe Val Trp Lys Leu Val Ala Asn Phe Arg Arg Gly Phe Arg Lys 515 520 525		
Glu Asp Arg Asn Gly Arg Asp Glu Met Asp Ile Glu Leu His Asp Val 530 535 540		
Ser Pro Ile Thr Arg His Pro Leu Gln Ala Leu Phe Ile Trp Ala Ile 545 550 555 560		
Leu Gln Asn Lys Lys Glu Leu Ser Lys Val Ile Trp Glu Gln Thr Arg 565 570 575		
Gly Cys Thr Leu Ala Ala Leu Gly Ala Ser Lys Leu Leu Lys Thr Leu 580 585 590		
Ala Lys Val Lys Asn Asp Ile Asn Ala Ala Gly Glu Ser Glu Glu Leu 595 600 605		
Ala Asn Glu Tyr Glu Thr Arg Ala Val Glu Leu Phe Thr Glu Cys Tyr 610 615 620		
Ser Ser Asp Glu Asp Leu Ala Glu Gln Leu Leu Val Tyr Ser Cys Glu 625 630 635 640		
Ala Trp Gly Gly Leu Glu His His His His His His 645 650		

&lt;210&gt; 676

&lt;211&gt; 132

&lt;212&gt; PRT

&lt;213&gt; Homo sapien

&lt;400&gt; 676

```

Thr Ala Ala Ser Asp Asn Phe Gln Leu Ser Gln Gly Gly Gln Gly Phe
1      5      10      15
Ala Ile Pro Ile Gly Gln Ala Met Ala Ile Ala Gly Gln Ile Arg Ser
      20      25      30
Gly Gly Gly Ser Pro Thr Val His Ile Gly Pro Thr Ala Phe Leu Gly
      35      40      45
Leu Gly Val Val Asp Asn Asn Gly Asn Gly Ala Arg Val Gln Arg Val
      50      55      60
Val Gly Ser Ala Pro Ala Ala Ser Leu Gly Ile Ser Thr Gly Asp Val
      65      70      75      80
Ile Thr Ala Val Asp Gly Ala Pro Ile Asn Ser Ala Thr Ala Met Ala
      85      90      95
Asp Ala Leu Asn Gly His His Pro Gly Asp Val Ile Ser Val Asn Trp
      100     105     110
Gln Thr Lys Ser Gly Gly Thr Arg Thr Gly Asn Val Thr Leu Ala Glu
      115     120     125
Gly Pro Pro Ala
      130

```

&lt;210&gt; 677

&lt;211&gt; 36

&lt;212&gt; DNA

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; PCR primer

&lt;400&gt; 677

ggggaattca tgatccggga gaaatttgcc cactgc

36

&lt;210&gt; 678

&lt;211&gt; 33

&lt;212&gt; DNA

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; PCR primer

&lt;400&gt; 678

gggctcgagt caggagttag agaccagcct ggc

33

&lt;210&gt; 679

&lt;211&gt; 675

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 679

```

atgcatcacc atcaccatca cacggccgcg tccgataact tccagctgtc ccaggggtggg 60
cagggattcg ccattccgat cgggcaggcg atggcgatcg cgggccagat caagcttccc 120

```

```

acggttcata tggggcctac cgccttcctc ggcttgggtg ttgtcgacaa caacggcaac 180
ggcgcaacgag tccaacgcgt ggtcgggagc gctcgggcgg caagtctcgg catctccacc 240
ggcgacgtga tcaccgcggt cgacggcgct ccgatcaact cggccaccgc gatggcggac 300
ggcgttaacg ggcatcatcc cgggtgaacgc atctcgggtg cctggcaaac caagtccggc 360
ggcagcgcga cagggaacgt gacattggcc gagggacccc cggccgaatt catgatccgg 420
gagaaatttg cccactgcac cgtgctaacc attgcacaca gattgaacac cattattgac 480
agcgcacaaga taatggtttt agattcagga agactgaaag aatatgatga gccgtatgtt 540
ttgctgcaaa ataaagagag cctatttttac aagatgggtg aacaactggg caaggcagaa 600
ggcgtgccc tcaactgaaac agcaaaacag agatggggtt tcaccatgtt ggccaggctg 660
gtctcaaaact cctga 675

```

&lt;210&gt; 680

&lt;211&gt; 291

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 680

```

atggggatcc gggagaaatt tgcccactgc accgtgctaa ccattgcaca cagattgaac 60
accattattg acagcgacaa gataatgggt ttagattcag gaagactgaa agaatatgat 120
gagccgtatg ttttgcgtga aaataaagag agcctatttt acaagatggg gcaacaactg 180
ggcaaggcag aagccgctgc cctcactgaa acagcaaaac agagatgggg ttccaccatg 240
ttggccaggc tgggtcctaaa ctccctcgag caccaccacc accaccactg a 291

```

&lt;210&gt; 681

&lt;211&gt; 1074

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 681

```

atgtcagcca ttgagagggt gtcagaggca atcgtcagca tccgaagaat ccagaccttt 60
ttgtactttg atgagatata acagcgcaac cgtcagctgc cgtcagatgg taaaaagatg 120
gtgcatgtgc aggattttac tgcttttttg gataaggcat cagagacccc aactctacaa 180
ggcctttcct ttactgtcag acctggcgaa ttgttagctg tggtcggccc cgtgggagca 240
gggaagtcat cactgttaag tgccgtgctc ggggaattgg cccaagtca cgggctggtc 300
agcgtgcatg gaagaattgc ctatgtgtct cagcagccct ggggtgttctc gggaaactctg 360
aggagtaata ttttatttgg gaagaaatac gaaaaggaa gatatgaaaa agtcataaag 420
gcttgtgctc tgaaaaagga ttacagctg ttggaggatg gtgatctgac tgtgatagga 480
gatcggggaa ccacgctgag tggaggcgag aaagcacggg taaaccttgc aagagcagtg 540
tatcaagatg ctgacatcta tctcctggac gatcctctca gtgcagttaga tgcggaagt 600
agcagacact tggtcgaact gtgtatttgt caaattttgc atgagaagat cacaatttta 660
gtgactcatc agttgcagta cctcaaagct gcaagtcaga ttctgatatt gaaagatgg 720
aaaatgggtg agaaggggac ttacactgag ttcttaaaat ctggtataga ttttggctcc 780
cttttaaaaga aggataatga ggaaagtga caacctccag ttccaggaa tcccacacta 840
aggaatcgta ccttctcaga gtcttcgggt tgggtctcaac aatcttctag accctccttg 900
aaagatgggt ctctggagag ccaagataca gagaatgtcc cagttacact atcagaggag 960
aaccgttctg aaggaaaagt tggttttcag gcctataaga attacttcag agctgggtgt 1020
cactggattg tcttcatttt ccttattctc gagcaccacc accaccacca ctga 1074

```

&lt;210&gt; 682

&lt;211&gt; 224

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 682

```

Met His His His His His His Thr Ala Ala Ser Asp Asn Phe Gln Leu
          5                      10                      15

```

```

Ser Gln Gly Gly Gln Gly Phe Ala Ile Pro Ile Gly Gln Ala Met Ala

```

20						25						30					
Ile	Ala	Gly	Gln	Ile	Lys	Leu	Pro	Thr	Val	His	Ile	Gly	Pro	Thr	Ala		
35						40						45					
Phe	Leu	Gly	Leu	Gly	Val	Val	Asp	Asn	Asn	Gly	Asn	Gly	Ala	Arg	Val		
50						55						60					
Gln	Arg	Val	Val	Gly	Ser	Ala	Pro	Ala	Ala	Ser	Leu	Gly	Ile	Ser	Thr		
65						70						75					
Gly	Asp	Val	Ile	Thr	Ala	Val	Asp	Gly	Ala	Pro	Ile	Asn	Ser	Ala	Thr		
85						90						95					
Ala	Met	Ala	Asp	Ala	Leu	Asn	Gly	His	His	Pro	Gly	Asp	Val	Ile	Ser		
100						105						110					
Val	Thr	Trp	Gln	Thr	Lys	Ser	Gly	Gly	Thr	Arg	Thr	Gly	Asn	Val	Thr		
115						120						125					
Leu	Ala	Glu	Gly	Pro	Pro	Ala	Glu	Phe	Met	Ile	Arg	Glu	Lys	Phe	Ala		
130						135						140					
His	Cys	Thr	Val	Leu	Thr	Ile	Ala	His	Arg	Leu	Asn	Thr	Ile	Ile	Asp		
145						150						155					
Ser	Asp	Lys	Ile	Met	Val	Leu	Asp	Ser	Gly	Arg	Leu	Lys	Glu	Tyr	Asp		
165						170						175					
Glu	Pro	Tyr	Val	Leu	Leu	Gln	Asn	Lys	Glu	Ser	Leu	Phe	Tyr	Lys	Met		
180						185						190					
Val	Gln	Gln	Leu	Gly	Lys	Ala	Glu	Ala	Ala	Ala	Leu	Thr	Glu	Thr	Ala		
195						200						205					
Lys	Gln	Arg	Trp	Gly	Phe	Thr	Met	Leu	Ala	Arg	Leu	Val	Ser	Asn	Ser		
210						215						220					

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<210> 683
<211> 357
<212> PRT
<213> Homo sapiens
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<400> 683
Met Ser Ala Ile Glu Arg Val Ser Glu Ala Ile Val Ser Ile Arg Arg
          5                      10                      15

Ile Gln Thr Phe Leu Leu Leu Asp Glu Ile Ser Gln Arg Asn Arg Gln
          20                      25                      30

Leu Pro Ser Asp Gly Lys Lys Met Val His Val Gln Asp Phe Thr Ala
          35                      40                      45

Phe Trp Asp Lys Ala Ser Glu Thr Pro Thr Leu Gln Gly Leu Ser Phe

```

270

50					55					60					
Thr	Val	Arg	Pro	Gly	Glu	Leu	Leu	Ala	Val	Val	Gly	Pro	Val	Gly	Ala
65					70					75					80
Gly	Lys	Ser	Ser	Leu	Leu	Ser	Ala	Val	Leu	Gly	Glu	Leu	Ala	Pro	Ser
				85					90					95	
His	Gly	Leu	Val	Ser	Val	His	Gly	Arg	Ile	Ala	Tyr	Val	Ser	Gln	Gln
			100					105					110		
Pro	Trp	Val	Phe	Ser	Gly	Thr	Leu	Arg	Ser	Asn	Ile	Leu	Phe	Gly	Lys
			115				120					125			
Lys	Tyr	Glu	Lys	Glu	Arg	Tyr	Glu	Lys	Val	Ile	Lys	Ala	Cys	Ala	Leu
	130					135					140				
Lys	Lys	Asp	Leu	Gln	Leu	Leu	Glu	Asp	Gly	Asp	Leu	Thr	Val	Ile	Gly
	145					150					155				160
Asp	Arg	Gly	Thr	Thr	Leu	Ser	Gly	Gly	Gln	Lys	Ala	Arg	Val	Asn	Leu
				165					170					175	
Ala	Arg	Ala	Val	Tyr	Gln	Asp	Ala	Asp	Ile	Tyr	Leu	Leu	Asp	Asp	Pro
			180					185					190		
Leu	Ser	Ala	Val	Asp	Ala	Glu	Val	Ser	Arg	His	Leu	Phe	Glu	Leu	Cys
			195				200					205			
Ile	Cys	Gln	Ile	Leu	His	Glu	Lys	Ile	Thr	Ile	Leu	Val	Thr	His	Gln
	210					215					220				
Leu	Gln	Tyr	Leu	Lys	Ala	Ala	Ser	Gln	Ile	Leu	Ile	Leu	Lys	Asp	Gly
	225					230					235				240
Lys	Met	Val	Gln	Lys	Gly	Thr	Tyr	Thr	Glu	Phe	Leu	Lys	Ser	Gly	Ile
				245					250					255	
Asp	Phe	Gly	Ser	Leu	Leu	Lys	Lys	Asp	Asn	Glu	Glu	Ser	Glu	Gln	Pro
			260					265					270		
Pro	Val	Pro	Gly	Thr	Pro	Thr	Leu	Arg	Asn	Arg	Thr	Phe	Ser	Glu	Ser
			275				280					285			
Ser	Val	Trp	Ser	Gln	Gln	Ser	Ser	Arg	Pro	Ser	Leu	Lys	Asp	Gly	Ala
			290				295				300				
Leu	Glu	Ser	Gln	Asp	Thr	Glu	Asn	Val	Pro	Val	Thr	Leu	Ser	Glu	Glu
	305					310					315				320
Asn	Arg	Ser	Glu	Gly	Lys	Val	Gly	Phe	Gln	Ala	Tyr	Lys	Asn	Tyr	Phe
				325					330					335	
Arg	Ala	Gly	Ala	His	Trp	Ile	Val	Phe	Ile	Phe	Leu	Ile	Leu	Glu	His
			340					345					350		
His	His	His	His	His											
			355												

<210> 684  
 <211> 96  
 <212> PRT  
 <213> Homo sapiens

<400> 684  
 Met Gly Ile Arg Glu Lys Phe Ala His Cys Thr Val Leu Thr Ile Ala  
                           5                          10                          15  
 His Arg Leu Asn Thr Ile Ile Asp Ser Asp Lys Ile Met Val Leu Asp  
                           20                          25                          30  
 Ser Gly Arg Leu Lys Glu Tyr Asp Glu Pro Tyr Val Leu Leu Gln Asn  
                           35                          40                          45  
 Lys Glu Ser Leu Phe Tyr Lys Met Val Gln Gln Leu Gly Lys Ala Glu  
                           50                          55                          60  
 Ala Ala Ala Leu Thr Glu Thr Ala Lys Gln Arg Trp Gly Phe Thr Met  
                           65                          70                          75                          80  
 Leu Ala Arg Leu Val Ser Asn Ser Leu Glu His His His His His His  
                           85                          90                          95

<210> 685  
 <211> 35  
 <212> DNA  
 <213> Artificial Sequence

<220>  
 <223> PCR primer

<400> 685  
 cgcccatggg gatccgggag aaatttgccc actgc 35

<210> 686  
 <211> 35  
 <212> DNA  
 <213> Artificial Sequence

<220>  
 <223> PCR primer

<400> 686  
 cgcctcgagg gagtttgaga ccagcctggc caaca 35

<210> 687  
 <211> 38  
 <212> DNA  
 <213> Artificial Sequence

<220>  
 <223> PCR primer

<400> 687  
gcacggaccca tatgtcagcc attgagaggg tgtcagag 38

<210> 688  
<211> 34  
<212> DNA  
<213> Artificial Sequence

<220>  
<223> PCR primer

<400> 688  
ccgctcagaga ataaagaaaa tgaagacaat ccag 34

<210> 689  
<211> 27  
<212> DNA  
<213> Artificial Sequence

<220>  
<223> PCR primer

<400> 689  
gttgaattca tgcacgggcc ccagggtg 27

<210> 690  
<211> 30  
<212> DNA  
<213> Artificial Sequence

<220>  
<223> PCR primer

<400> 690  
cccctcagat cactatgggc tgccctcttga 30

<210> 691  
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<212> DNA  
<213> Homo sapiens

<400> 691  
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accgttcata tccggccctac cgccttcctc ggcttggttg ttgtcgacaa caacggcaac 180  
ggcgacagag tccaacgcgt ggtcgggagc gctccggcgg caagtctcgg catctccacc 240  
ggcgacgtga tcaccgcgtt cgacggcgct ccgatcaact cggccaccgc gatggcggac 300  
gcgcttaacg ggcatcatcc cggtgacgtc atctcgggtg cctggcaaac caagtcgggc 360  
ggcacgcgta cagggaacgt gacattggcc gagggacccc cggccgaatt catgcacggg 420  
ccccagggtc tggcacgctg ctccgagttg gcttggtcctg ccttggtctg cacctctgcg 480  
ggggtgcgtc tggagggggg ggaccggcca ccaaccttac ccagtcaagg aagtggatgg 540  
ccatgttccc acagcctgag tggctgccac ctgatggctg atggagcaaa ggccttagga 600  
aaagcagatg gcccttggcc ctaccttttt gttagaagaa ctgatgttcc atgtcctgca 660  
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<210> 692
<211> 304
<212> PRT
<213> Homo sapiens
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<400> 692

Met His His His His His His Thr Ala Ala Ser Asp Asn Phe Gln Leu  
5 10 15

Ser Gln Gly Gly Gln Gly Phe Ala Ile Pro Ile Gly Gln Ala Met Ala  
20 25 30

Ile Ala Gly Gln Ile Lys Leu Pro Thr Val His Ile Gly Pro Thr Ala  
35 40 45

Phe Leu Gly Leu Gly Val Val Asp Asn Asn Gly Asn Gly Ala Arg Val  
50 55 60

Gln Arg Val Val Gly Ser Ala Pro Ala Ala Ser Leu Gly Ile Ser Thr  
65 70 75 80

Gly Asp Val Ile Thr Ala Val Asp Gly Ala Pro Ile Asn Ser Ala Thr  
85 90 95

Ala Met Ala Asp Ala Leu Asn Gly His His Pro Gly Asp Val Ile Ser  
100 105 110

Val Thr Trp Cln Thr Lys Ser Gly Gly Thr Arg Thr Gly Asn Val Thr  
115 120 125

Leu Ala Glu Gly Pro Pro Ala Glu Phe Met His Gly Pro Gln Val Leu  
130 135 140

Ala Arg Cys Ser Glu Cys Ala Cys Pro Ala Leu Ala Ala Thr Ser Ala  
145 150 155 160

Gly Val Arg Leu Glu Gly Val Asp Arg Pro Pro Thr Leu Pro Ser Gln  
165 170 175

Gly Ser Gly Trp Pro Cys Ser His Ser Leu Ser Gly Cys His Leu Met  
180 185 190

Ala Asp Gly Ala Lys Ala Leu Gly Lys Ala Asp Gly Pro Trp Pro Tyr  
195 200 205

Leu Phe Val Arg Arg Thr Asp Val Pro Cys Pro Ala Ala Ser Glu Val  
210 215 220

Gly Gly Cys Ala Pro Ser Ser Trp Arg Ala Leu Ala Glu Val Thr Gly  
225 230 235 240

Cys Ser Leu Gly Pro Leu Gly Leu Ala Gln His Ala Gln Ala Ser Val  
245 250 255



Leu Leu Leu Cys Tyr Lys Trp Ser His Ile Gly Glu Thr Ser Ser His  
 260 265 270

Leu Arg Ser Lys Val Tyr Ala Ala Phe Gly Gly Ser Ser Pro Cys Leu  
 275 280 285

Lys Gly Leu Met Ser Leu Trp Ala Ser Trp Leu Ser Arg Gly Arg Pro  
 290 295 300

<210> 693

<211> 24

<212> DNA

<213> Artificial Sequence

<220>

<223> PCR primer

<400> 693

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24

<210> 694

<211> 29

<212> DNA

<213> Artificial Sequence

<220>

<223> PCR primer

<400> 694

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29

<210> 695

<211> 166

<212> PRT

<213> Homo sapiens

<220>

<221> VARIANT

<222> (1)...(166)

<223> Xaa = Any Amino Acid

<400> 695

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 His Pro Glu Tyr Asn Arg Pro Leu Leu Ala Asn Asp Leu Met Leu Ile  
 20 25 30  
 Lys Leu Asp Glu Ser Val Ser Glu Ser Asp Thr Ile Arg Ser Ile Ser  
 35 40 45  
 Ile Ala Ser Gln Cys Pro Thr Ala Gly Asn Ser Cys Leu Val Ser Gly  
 50 55 60  
 Trp Gly Leu Leu Ala Asn Gly Arg Met Pro Thr Val Leu Gln Cys Val  
 65 70 75 80  
 Asn Val Ser Val Val Ser Glu Glu Val Cys Ser Lys Leu Tyr Asp Pro

	85		90		95
Leu Tyr His Pro Ser Met Phe Cys Ala Gly Gly Gln Xaa Gln Xaa					
	100		105		110
Asp Ser Cys Asn Gly Asp Ser Gly Gly Pro Leu Ile Cys Asn Gly Tyr					
	115		120		125
Leu Gln Gly Leu Val Ser Phe Gly Lys Ala Pro Cys Gly Gln Val Gly					
	130		135		140
Val Pro Gly Val Tyr Thr Asn Leu Cys Lys Phe Thr Glu Trp Ile Glu					
	145		150		155
Lys Thr Val Gln Ala Ser					160
	165				

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 <211> 504  
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<220>  
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tctgacacca tccggagcat cagcattgct tgcagtgcc ctaccgcggg gaactcttgc	180
ctcgtttctg gctggggtct gctggcgaac ggcagaatgc ctaccgtgct gcagtgcgtg	240
aacgtgtcgg tgggtgtctga ggaggtctgc agtaagctct atgaccgct gtaccacccc	300
agcatgttct gcgccggcgg agggcaanac cagaangact cctgcaacgg tgactctggg	360
gggcccttga tctgcaacgg gtacttgcag ggccttgtgt ctttcggaaa agccccgtgt	420
ggccaagtgt gcgtgccagg tgtctacacc aacctctgca aattcactga gtggatagag	480
aaaaccgtcc aggccagtta atga	504

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 <213> Artificial Sequence

<220>  
 <223> PCR primer

<400> 697	
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<210> 698  
 <211> 35  
 <212> DNA  
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<220>  
 <223> PCR primer

<400> 698	
ctatagaatt cattaccaa aagctgggct ccagc	35

<210> 699